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4036

Scarlet Fever Immunity Reactions in Relation to Allergy.

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In a study of the reaction of children to Dr. Larsen's ricinoleated scarlet fever antigen, as determined by the Dick test, a wide diversity of response has been noted. Frequently children with positive Dick tests developed negative skin reactions, sometimes as early as 4 days, following the administration of antigen, but a return to the original state of skin sensitivity was observed in the majority in 6 to 8 weeks. Only a very few remained negative for as long as 6 months.

The variation in response is partially indicated by the following cases:

TABLE I.

	Original Skin Reaction	Skin reaction at subsequent intervals after antigen administration.		
No. 20	+	1 Month —	4 Months +	
No. 33	+	2 Weeks —	1 Month ±	6 Weeks ++
No. 60	+	4 Days ++	16 Days +	28 Days —
No. 70	+++	10 Days +	4 Weeks ±	5 Weeks +
No. 66	++	10 Days —	6 Weeks —	3 Months +
No. 67	++	10 Days —	6 Weeks +	3 Months +
No. 69	— (on 2 occasions)	4 Days ±	2 Weeks +	

Following antigen administration a decrease in reaction was noted in almost all who originally showed a markedly positive test. In a small number of cases 2 doses of antigen or even 3 failed to produce a negative test, or at least one which persisted over periods varying from 3 weeks to 3 months. An increase in reaction was noted frequently after the giving of antigen, which as a rule tended later to decrease, but in individuals who were originally slightly sensitive might be marked and persistent.

Infants very rarely gave a positive reaction and were frequently negative to as much as 20 skin test doses. One infant, 2 weeks old, whose skin reaction was negative to 50 S. T. D., developed temporarily a positive Dick test, 16 days after the last portion of 900 S. T. D. of scarlet fever toxin (so-called) had been given.

The diversity of skin reaction, as indicated by the Dick test, following antigen administration, seems to find no parallel in the phenomena of true toxin reactions and antitoxin production. Nor does the development of a positive test in an infant previously negative, in response to treatment with scarlet fever streptococcus filtrate find its explanation on any but an allergic basis. Our observations support the view that susceptibility to scarlet fever is concerned with an allergic factor; that infants, born non-sensitive, develop a sensitivity through frequent contact and close association with the streptococcus, and that the Dick test gives some indication of the degree of the sensitivity. Under sufficient stimulation the body cells may react to such an extent as to mask the allergic state. A negative Dick test may signify that an individual has not yet been sensitized, or has been sufficiently stimulated to have developed circulating antibodies, which mask the allergy.

4037

Effect of Acidosis in Strychnine Poisoning.

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From the Zoological Laboratory, State University of Iowa.

It has been demonstrated by a number of investigators that changes in the reaction of the blood toward the acid side prevent the clonic contraction and spasticity of the skeletal muscles in parathyroid tetany. The experiments reported here show that a decrease in the pH of the blood produced prior to the administration of lethal doses of strychnine, prevents violent tetanus, convulsions and death.

Acidosis was produced in 7 dogs by subcutaneous injections of nephro-toxic substances such as uranium nitrate and sodium tartrate. When the pH of the blood dropped to about 7.2 and the CO_2 capacity to around 22 volumes %, the dogs received subcutaneously 1/160 gr. per kilo of strychnine sulphate. Ten minutes later slight muscle tremors and spasms developed. In all cases recovery occurred within 45 minutes. One dog died 1 hour following injection of the lethal dose of strychnine. In this case death was apparently due to uranium nitrate poisoning.

In other series of dogs acidosis was produced by means other than those involving impairment of renal function. This was brought about by administering NH_4Cl to one series of animals and CO_2 to another. Muscle spasms from which the dogs soon recovered, followed the injections of a lethal dose of strychnine.

Control dogs receiving the same lethal dose of strychnine died in convulsions within 1 hour.

From the results we obtained it is evident that it is the initial drop in pH occurring before injection of the strychnine and not the fall produced by convulsions and the resulting anoxemia that is effective in preventing convulsions and death from strychnine poisoning. The data from 1 of our experimental and 1 of our control dogs are presented in Table I.

TABLE I.

Animal	Date	Time	Strychnine given in gr.	pH	CO_2 capacity vol. %	Remarks
Dog 12 14 kilo	Feb. 28	10:30 A.M.		7.39	46.8	Given 100 cc. 5% solution NH_4Cl by stomach tube.
		1:30 P.M.		7.19	21.1	
		2:45 P.M.	7/80			
		2:55—3:20 P.M.				Spasms and muscle twitching.
		3:23 P.M.		7.04	17.5	
		3:35 P.M.				Recovered. Remained normal.
Dog 3C 8.75 kilo	Feb. 27	3:00 P.M.		7.38	43.2	
		4:10 P.M.	1/20			
		4:20 P.M.				Violent convulsions.
		4:40 P.M.		6.92	28.3	Violent convulsions.
		5:20 P.M.				Died in convulsions.

4038

Anemia Following Administration of Brilliant Vital Red.

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From the Department of Physiology, State University of Iowa.

During experiments upon dogs in which brilliant vital red was administered, there appeared after a time an anemia. The use of this dye for clinical purposes as well as the recent work on the protective power of this and other dyes against certain toxins gives an added interest in any effect of this substance. This paper presents the data of certain effects which this dye has had upon the blood picture of dogs.

Several normal dogs were used, with controls for nutritional variations and hemorrhage. In each the body weight, red and white cell counts, cell volume, stained blood smears and hemoglobin determinations were made to establish normals. The hemoglobin was estimated both by the Newcomer colorimetric and the Van Slyke oxygen capacity methods. Blood for these determinations was drawn from the jugular vein. The amount of dye* used in each case was an intravenous injection of 15 mg. per kg. of body weight. The number of doses given and the intervals between them were varied according to the response which each animal made. Some dogs reacted readily and others were more refractory to the substance.

There appeared in no instance any immediate or delayed toxic or other systemic effects attributable to the dye other than that of the blood picture. The weights of the 7 dogs remained practically the same throughout the experiment.

There was no demonstrable fall of the blood constituents during the first 10 or 12 hours, but the tendency toward anemia began usually within 1 or 2 days and continued thereafter for several days. The maximum loss in most cases occurred at the 3rd or 4th day, after which there was a slow recovery. The hemoglobin value and the red corpuscle count fell together, but in each case the hemoglobin value dropped slightly faster than the red count, thereby progressively diminishing the color index. There was also a corresponding decrease in cell volume. In our most striking case, following 1 injection of the dye in the dosage and manner mentioned, the hemoglobin value fell in 4 days to 66% of its original amount, and the red count to 79% of its normal. In the other animals there were losses varying from that stated above to a fall of 83% of its initial amount in the course of 8 weeks with administrations of the dye at intervals of 2 or 3 weeks. In this animal the red blood corpuscle count remained practically the same throughout the experiment.

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* Brilliant Vital Red (Evans) National Aniline and Co.

Examinations of blood smears show progressive achromia paralleling the hemoglobin loss. Changes in the size, shape and staining reaction of the red cells were noted early in some and later in others, without apparent relation to the rate or degree of hemoglobin loss.

The white blood count varied from time to time in the same animal, but all the counts remained within normal limits for each animal. The smears studied showed nothing extraordinary, except that after dye injection it seemed that the small lymphocytes were rarer than before; there were no constant signs of effect of the dye upon any of the leucocytic series as demonstrable by the smear.

It may be well to bear this rather unsuspected effect in mind when clinical and experimental studies based upon the assumption that it is an inert substance are being made.

4039

Effect of High Temperature on the Gonads of Frog Larvae.

EMIL WITSCHI.

From the Zoological Laboratory, University of Iowa.

Frog larvae *(R. sylvatica)* which had been raised under nearly optimal conditions up to the 7th week were subjected after the 34th day to the maximal temperature they can endure permanently, *i. e.,* 32° C. The gonads of both males and females grow much slower than those of normal controls. However, the spermatogonia of the testis are of about normal size and the seminiferous tubules differentiate in a typical way. The reactions of the ovaries are more complex and more important. At the time when the temperature was raised the ovaries contained large numbers of young ovocytes in the synapsis stage. Two weeks later this type of germ cells has completely disappeared. The ovogonia are still present and the deeper layers of the cortex contain now large auxocytes. The latter, however, are in way of degeneration. Their nucleoli are extremely large and basophilic and the ovoplasm contains coarse granules. During 2 more weeks the eggs disappear completely, the ovogonia being the only germ cells spared from degeneration.

Immediately after the differentiation of further ovocytes has come to an end, the medullary part of the ovaries starts to grow rapidly. Within a few weeks the ovarial sac *(rete ovarii)* transform into a typical rete testis, vasa efferentia and seminiferous tubules. At first the latter lack completely any germ cells. However, sooner or later the ovogonia migrate from the cortex to the medulla, and after having entered the seminiferous tubules transform into spermatogonia.

Thus the experiment leads to the total reversal of sex of the females. The normal controls consisted of 100 females and 96 males. The experimental group contained no typical females after the 2nd week of rise in temperature; but between the 15th and the 33rd day 53 females in different stages of sex transformation and 62 typical males were preserved.

4040

Interrelation of Pituitary and Thyroid in Metamorphosis of Neotenic Amphibians.

W. R. INGRAM. (Introduced by W. W. Swingle.)

From the Zoological Laboratory, State University of Iowa.

While it has been known for some time that transplants of anterior lobe of the pituitary of adult frogs would cause accelerated growth in small tadpoles[1] no attempt has been made to show the relation of this gland to the condition of partial neoteny existing in some anurans. Neotenic amphibians exhibit prolonged retention of larval form. Total neoteny, of which the Mexican axolotl is an example, is characterized by the failure of such animals to metamorphose spontaneously. Among the anurans *Rana catesbiana* and *Rana clamata* show greatly prolonged larval stages which mark them as partially neotenic types. In the totally neotenic axolotl, metamorphosis upon injection of anterior lobe extracts has been reported by some workers[2, 3] and denied by others.[4]

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[1] Allen, B. M., *J. Physiol. Zool.*, 1928, i, 153.

[2] Hogben, L. T., *Proc. Roy. Soc. B.*, 1923, xciv, 204.

[3] Uhlenhuth, E., *Brit. J. Exp. Biol.*, 1927, v, 1.

[4] Smith, P. E., *Brit. J. Exp. Biol.*, 1926, iii, 239.

The anterior lobe of adult *Rana pipiens* was transplanted intraperitoneally into *Rana clamata* larvae of various stages of limb development—up to a hind-limb length of 5 mm. Three transplants were made at weekly intervals into 35 tadpoles, allotted according to size into cultures of 5. Controls of approximately the same development were injected into bits of muscle. After the 2nd transplant marked limb growth was noted; the general growth being accelerated to any extent only in the smaller tadpoles.

After the 12th day following the first transplantation marked metamorphic signs appeared, and in from 25 to 33 days forelimbs began to break through and tail atrophy was observed. Most of the experimental animals were killed when they showed practically complete metamorphosis and the thyroids removed for examination. The control animals exhibited only a slight normal growth and development and in no case showed any signs of metamorphosis.

Pronounced development of the thyroids of the treated animals was found—in some cases their diameter was twice that of the control glands. Sections of the control glands displayed large, colloid-filled follicles with walls composed of flat, inactive-appearing cells. The thyroid of treated animals, on the other hand, showed considerable loss of colloid substance from the follicles with collapse of some of the latter, and extreme activity of the cells which were greatly elongated, with proportionate thickening of the follicle walls. Freeing of colloid and heightened activity were evidently effects of the anterior lobe transplants.

The histological picture approximates that found by Uhlenhuth[5] in the thyroids of normally metamorphosing salamanders and in the case of one axolotl treated with anterior lobe powder.

The evidence would indicate that the neotenic condition in certain anurans depends upon a defective relationship between the anterior lobe of the pituitary and the thyroid. Whether this depends upon a retarded anterior lobe development or upon a failure to release the anterior lobe active principle may be shown by subsequent experiments.

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[5] Uhlenhuth, E., *Roux' Arch. Entw.*, 1927, cix, 671.

4041

Comparison of Rates of Killing of Parthenogenetic and Sexual Forms of Daphnia magna at Higher Temperatures.

L. A. BROWN.

From the Zoological Laboratory, State University of Iowa.

In a recent paper[1] the temperature characteristics for the rate of killing of 2 species of cladocerans were reported. One of these species, *Moina macrocopa,* yielded a value of the temperature characteristic equal to about 108,500 calories, for the temperature interval of 42° to 47° C. The second species, *Daphnia pulex,* yielded a slightly higher value, 119,500 calories, for the temperature interval 32° to 37° C. The animals used in these experiments were adult parthenogenetic females. The present paper presents data for the parthenogenetic females of a 3rd species, *Daphnia magna,* and an account of a comparison of this parthenogenetic form with the sexual females and the adult males of the same species.

The procedure used in determining the rate of killing in the present case was the same as that described in the paper just referred to. Curves of the velocities of killing at each of several lethal temperatures were determined separately for the 3 forms used. The parthenogenetic females were reared from young females placed in plenty of food. The males were reared as young from parthenogenetic females which previously had been somewhat crowded together in rich food; the sexual females were obtained by crowding females together in weak food. The rate of killing was taken as the reciprocal of the time necessary to kill 50% of the animals (Table I). To determine the temperature characteristic, the logarithms of these rates were plotted against the reciprocals of the absolute temperatures (Fig. 1) and the value of the constant μ calculated from the slope of the line drawn through the plotted points according to the equation,

$$K_2/K_1 = e(\mu/R)\ (1/T_1 - 1/T_2)$$

where K_1 and K_2 are proportional to velocity constants at the respective temperature T_1 and T_2, R the gas constant, and μ the critical thermal increment or temperature characteristic.[2]

The graphs show that the thermal increment for the parthenogenetic and sexual females is practically the same, with μ equal to 187,700 calories. The plotted line gives a better fit for the parthe-

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[1] Brown, L. A., and Crozier, W. J., *J. Gen. Physiol.,* 1927, xi, 25.

[2] Crozier, W. J., *J. Gen. Physiol.,* 1924, vii, 123.

TABLE I.

Showing data for rates of killing of parthenogenetic females, sexual females and males of *Daphnia magna* at temperatures 35° to 41° C. The times given are those for 50% dead. The durations of exposure at each temperature ranged from those that killed 100% down to those that failed to kill the animals at all.

°C		Number of animals	Time in seconds	1/time x 10^4 (Rate)
35	Parthenogenetic females	376	5280	1.89
	Sexual females	238	7200	1.39
	Males	251	8160	1.23
36	Parthenogenetic females	503	2460	4.07
	Sexual females	204	4860	2.06
	Males	175	3600	2.78
37	Parthenogenetic females	430	600	16.7
	Sexual females	272	1440	6.94
	Males	560	1440	6.94
38	Parthenogenetic females	504	260	38.5
	Sexual females	275	336	29.8
	Males	386	288	34.7
39	Parthenogenetic females	409	104	96.2
	Sexual females	168	118	84.7
	Males	145	56	179.0
40	Parthenogenetic females	350	40	250.0
	Sexual females	148	65	154.0
	Males	161	33	303.0
41	Parthenogenetic females	335	23	435.0

nogenetic females than for the sexual females. This may be due in part to the fact that fewer animals were used in determining the velocities of killing in the latter form, but probably is due to the greater difficulty in getting animals of equivalent ages in the case of the ephippial females. The thermal increment for the males is somewhat different than that for the females, due to the presence of a "break"[3] at 37°. The exact slope of the graphs above and below this point cannot be given much weight, because the temperature range is limited. On the whole the sexual female more nearly resembles the parthenogenetic female, according to its temperature characteristic, than it does the other sexual form, the male.

It is interesting to note that data for the parthenogenetic females of this species from earlier work of v. Transehe,[4] when plotted in the same manner, shows a break at 38° with a comparable value (177,500) of the temperature characteristic above this temperature. An exact comparison cannot be made, however, as he used a different end point for the death of his animals than was used in the present experiments.

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[3] Crozier, W. J., *J. Gen. Physiol.*, 1925, ix, 525.

[4] von Transehe, N., *Arch. ges. Physiol.*, 1913, cliii, 323.

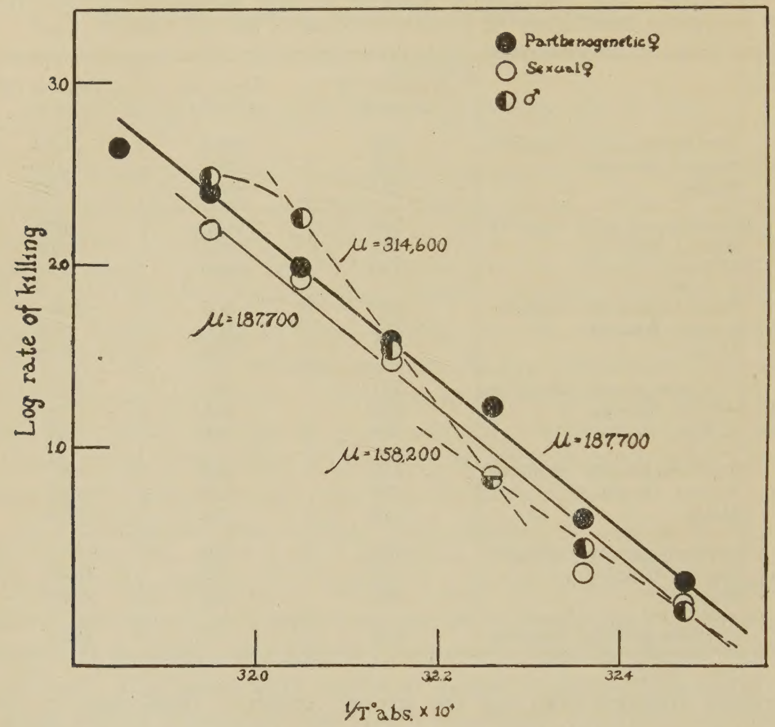

FIG. 1.

Logarithms of the rates of killing (see Table I, last column) of parthenogenetic females, sexual females, and males of *Daphnia magna* plotted against the reciprocals of the absolute temperatures. The temperatures Centigrade range from 35° to 41°. The values of the thermal increments (μ) are calculated from the equation given in the text.

4042

Nitrogen and Sulfur Metabolism of Diabetic Children.

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(Introduced by J. D. Boyd.)

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The excretion of nitrogen and sulfur in the urine of 36 diabetic children of from 2 to 15 years of age has been studied in an attempt to gain more information concerning the protein metabolism of controlled diabetic children on diets high in protein. With a very few exceptions, these children were receiving approximately 2 gm. of protein per kilo body weight, the ratio of the gm. of nitrogen per gm. of sulfur in the different diets varying from 10.3 to 13.4. Data were collected during a total of 47 periods of 3 to 4 days each.

The N :S ratios of the urines approximate those of the diet rather closely (ranging from 10.9 to 16.6), with a definite tendency to be slightly higher. Children who were much underweight and were gaining rapidly showed the largest increases, while 4 rather fat, phlegmatic children showed urinary N:S ratios almost identical with those of the diets. Three adolescent girls, whose urinary N :S ratios were but slightly above the diet ratio, were kept on a lower protein diet (1 gm. per kilo) for about 3 months. At the end of this time the N balances were barely positive, but the N :S ratios of the urines were definitely increased.

These data have been interpreted as indicating a slight but definite tendency on the part of the growing child to retain a sulfur-rich protein for anabolic needs.

4043

Fat Absorption on High Fat Diets.

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The subjects of this study were 31 diabetic children, from 2½ to 15 years of age. Food with a caloric equivalent sufficient for full activity was provided, supplied chiefly as fat, with a potential fatty-acid: glucose weight ratio of 1½ :1. In most instances, patients were aglycosuric. Three day collections were made under expert supervision, using the usual technique. In some instances the total fecal output was dried and finely ground before analysis; in others aliquot portions of the output, thoroughly mixed, were analyzed without preliminary drying. Total fat was determined according to a modification of a method suggested by Eckstein[1] as most suitable for the purpose. In general it consists of prolonged dehydration and extraction with successive quantities of absolute alcohol, followed by chloroform. The combined extracts after evaporation to dryness in the cold are extracted with petroleum ether, the extract filtered, desiccated and weighed. Known amounts of butter oil were recovered with but small error by this method.

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[1] Eckstein, H. C., personal communication.

The average total daily output of the ether-soluble substances was 4.43 gm. per child. Compared with the individual daily intake, the excretion was equivalent to from 0.75% to 6.5% of the amount of fat ingested, with an average value of 2.56%. These patients were receiving daily approximately 3 gm. of fat per pound of body weight, constituting about 75% of the total calories. The retention is similar to that found in children receiving the usual fat intake, which comprises about 30% of the total calories.

This study confirms the observations of others that fat absorption in the healthy person is practically complete, even with a high fat intake. It also indicates that the adequacy of fat digestion in diabetic children is not demonstrably diminished.

4044

Glycogen Formation under Amytal Anaesthesia.

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From the Department of Physiology, State University of Iowa.

In a previous report[1] it was pointed out that dogs under amytal anesthesia exhibited a decreased capacity to assimilate injected glucose. Preliminary to a study of factors influencing the distribution of injected glucose, it was desirable to know whether this effect of amytal was a quantitative one affecting all tissues or whether its effect was limited primarily to certain tissues.

A comparison of glycogen formation in the unanesthetized and anesthetized (amytal) animal has been made in experiments on 8 dogs. Samples of liver and muscle tissue frog glycogen determinations were quickly removed under light ethylene anesthesia. One hour later glucose was injected at the rate of 3 gm. per kilo of body weight per hour for a period of 3 hours. One hour later when the blood sugar had returned to approximately its original value, samples of tissue were removed from the opposite side for analysis.

It was found that approximately the same increase in muscle glycogen had occurred in animals with or without amytal anesthesia. (Table I.) However, the increase in liver glycogen was over twice as great in the unanesthetized animals as in the experiments in which the glucose injections were made under amytal anesthesia. Because of this finding we believe that animals under this anesthetic are not suitable for experimentation in problems concerning carbohydrate storage.

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[1] Hines, H. M., Boyd, J. D., and Leese, C. E., *Am. J. Physiol.*, 1926, lxxvi, 293.

TABLE I.
Glycogen increase in gm. per 100 gm. of tissue.

With amytal			Without amytal		
No.	Liver	Muscle	No.	Liver	Muscle
1	1.73	.95	5	4.39	.63
2	2.63	.20	6	5.72	.59
3	1.59	.54	7	4.16	.18
4	2.23	.20	8	3.52	.52
Avg.	2.05	.47	Avg.	4.45	.48

4045

Effect of Pituitrin Administration on Rate of Disappearance of Injected Substances.

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From the Department of Physiology, State University of Iowa.

In previous investigations by the authors,[1, 2] it was found that pituitrin administration resulted in a decreased rate of removal of injected fluid and glucose by the tissues of the unanesthetized dog. This report is concerned with the effect of pituitrin on the removal from the blood stream of intravenously injected chlorides and a colloidal dye, Brilliant Vital Red. The former is of interest because the work of other investigators tended to show that the diuretic-antidiuretic action of pituitrin may be due to an effect on electrolyte distribution.

Unanesthetized dogs deprived of food and water for a period of 20 hours were injected with an isotonic or hypertonic (5 times isotonic) Ringer's solution at a rate of 15 or 25 cc. per kilo body weight per hour by the continuous intravenous method. At times commercial pituitary extracts in amounts of .05 to .08 cc. per kilo

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[1] Hines, H. M., Leese, C. E., and Boyd, J. D., *Am. J. Physiol.*, 1927, lxxxi, 27.

[2] Hines, H. M., Leese, C. E., and Jacobs, H. R., *Am. J. Physiol.*, 1927, lxxxiii, 269.

per hour were added to this solution. Studies were made of plasma chloride changes, chloride output in urine and relative blood volume changes as calculated from hemoglobin and plasma protein changes. The amount of chlorides retained by the tissues was calculated from the difference between the amount injected and that present in urine and blood. The small amount of chlorides that the animal would have eliminated without chloride administration has been neglected in these calculations. The effect of pituitrin on rate of disappearance of Brilliant Vital Red from the blood was determined by comparing the plasma dye concentration following the injection of 15 mg. per kilo of body weight at intervals of 1/10, 1½, 3½, 6 and 9 hrs. after its administration. Controls were run on all animals and the order of the control and pituitrin experiments was alternated in the different animals.

When isotonic Ringer's solution was injected for a period of 2 hours the plasma chlorides showed an average increase of 34 mg. (NaCl) as compared to an increase of 43 mg. in the same animals with Ringer's and pituitrin. When hypertonic Ringer's was injected the increase was 89 and 144 mg. respectively. Table I summarizes the average values obtained for the distribution of the injected chlorides in experiments on 6 animals. It is to be noted the effect of pituitrin was to lessen the amount of chlorides taken up by the tissues from the blood stream. This effect is more marked in the experiments with isotonic solutions. Little effect was noted on the amount of chlorides eliminated by kidney. This suggests an extra renal action of pituitrin as being the major factor involved. In the experiments with isotonic Ringer's solution the urine chloride concentration averaged 1.96% (NaCl) as compared to 1.53% with Ringer's and pituitrin. In the experiments with hypertonic solutions the concentrations averaged 1.57% and 2.08% respectively. Pituitrin administration was found to retard the rate of removal of

TABLE I.
Distribution of Injected Chlorides (Averages).

Nature of Injection	% excreted during injection period	% found in blood stream*	% calculated to enter tissues*	% excreted in 3 hr. post injection period
Isotonic Ringer's	29.1	27.2	43.7	34.4
Isotonic Ringer's and Pituitrin	27.4	48.7	23.9	45.5
Hypertonic Ringer's	14.0	27.3	58.7	61.9
Hypertonic Ringer's and Pituitrin	23.4	33.6	43.0	57.7

* At the end of the injection period.

Brilliant Vital Red from the blood stream in experiments on 5 out of 8 animals. Experiments on 3 animals showed no appreciable effects. Blood volume as determined by hemoglobin changes was not altered in the Vital Red studies. These and previous findings lend support to the idea that many of the effects of pituitrin administration are due to a lessened exchange of material between the blood and tissues.

4046

Effect of Various Ions upon the Heart Rhythm of Crayfish (Cambarus clarkii).

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From the Zoological Laboratory, State University of Iowa.

Using perfusing solutions of various salts approximating in ionic concentrations those found by Griffith[1] to be present in the blood of *Astacus fluviatilis,* an attempt was made to determine the effect of the Na, K, Ca, and Mg ion upon the intact heart of the Crayfish *(Cambarus clarkii).* For comparative purposes a control perfusing solution containing 1% NaCl+0.028%—KCl+0.024% $CaCl_2$ was employed. Such a solution applied to the heart maintained the normal rhythm for a period of several hours when perfused at a temperature of 25±0.1 degrees centigrade. Graphic records were obtained of the heart rhythm while being perfused with the various solutions.

In determining the effect of the Na ion, 3 perfusing solutions were employed, viz.: A pure solution of 1% NaCl, one containing 2% NaCl+0.028% KCl+0.024% $CaCl_2$ and one containing 0.028% KCl+0.024% $CaCl_2$. Both solutions containing Na produced a marked increase in rate and amplitude of the beats coupled with a loss in tone. The pure 1% solution had an especially marked effect upon the tone. The solution lacking Na produced a sharp increase in the tone accompanied by a loss in amplitude and rate, the heart generally stopping in diastolic arrest in less than 20 minutes. It may be noted in this connection that Carlson,[2] working upon Limulus, found that the Na stimulates the heart and increases the amplitude of the beats. Hogben[3] noted that in Maia and Homarus a pure solution of NaCl produced an almost immediate increase in tone, resulting shortly in systolic arrest. Rogers[4] observed that NaCl had the power of restoring rhythmatic contractions in the heart of the crab *(Brachnotus nudus)*. It is concluded from the present work that the Na ion increases the rate and amplitude and decreases the tone of the crayfish heart and is, therefore, concerned in the regulation of normal heart rhythm.

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[1] Griffith, A. B., "The Physiology of the Invertebrata." New York, 1892.

[2] Carlson, A. J., *Ergebnisse der Physiol.*, 1909, viii, 372.

[3] Hogben, L. T., *Quar. J. Ex. Physiol.*, 1925, xv, 263.

Similar experiments were performed with solutions of KCl and $CaCl_2$. A pure solution of 0.024% $CaCl_2$ produced a sharp increase in tone and a slight decrease in the rate. Increasing the $CaCl_2$ the control perfusing solution affected the rate only, the latter being decreased slightly. A pure solution of 0.028% KCl invariably depressed the rate and amplitude but had slight if any effect upon the tone. The removal of K from the control perfusing solution resulted in systolic arrest of the heart in less than 30 minutes. Normal rhythm could subsequently be restored only upon the replacement of KCl in the perfusing solution. In regard to the effect of K and Ca upon the heart rhythm of other closely related species, Hogben[3] finds that in Maia an excess of K produces systolic arrest of the heart. Carlson[2] observed that K and Ca both produced depressor action upon Limulus heart muscle. The present work is similar to the above in that K and Ca depress the rate and amplitude and increase the tone of the Crayfish heart, the Ca ion having an especially pronounced effect upon the tone.

The intact heart of the Crayfish was found to beat normally in the absence of Mg from the perfusing solution. Small additions of $MgCl_2$ to the control perfusing solution had no effect upon the normal rhythm. However, when the concentration of $MgCl_2$ was considerably increased (to about 0.1%) the rate decreased somewhat. The results obtained indicate that the Mg ion is not essential for the maintenance of normal heart rhythm in the Crayfish.

Normal perfusing solutions in which the hydrogen ion concentration had been altered by means of HCl, CO_2, and NaOH produced no marked effects upon the normal heart rhythm within the range of pH 5.5 to 9.0. Decreasing the pH below 5.5, however, resulted in a marked increase in tone. Hogben[3] likewise noted that the hearts of *Homerus* and *Maia* were extremely insensitive to changes in hydrogen concentration and that the heart would continue to function normally in a perfusing solution having a pH as low at 5.6. It is evident, therefore, from the present results, that the crayfish heart is capable of marked adaptation in this respect and can maintain its normal rhythm within a considerable range of hydrogen ion concentration.

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[4] Rogers, C. G., *J. Exp. Zool.*, 1905, ii, 237.

Western New York Branch.

University of Rochester, May 12, 1928.

4047

A Method of Graphic Registration of Heart Sounds.

C. J. CAMPBELL. (Introduced by F. P. Knowlton.)

From the Laboratory of Physiology, College of Medicine, Syracuse University.

The method is an adaptation of the "ultramicrometer" described by Dowling.[1] A Hartley circuit is used. A condenser microphone and 2 "pancake" inductance coils of 85 and 100 turns each form the oscillating circuit.

Because the electrical changes to be recorded are of relatively short duration, the "zero shunt" described by Dowling is not used. A variable non-inductive resistance is placed in the plate circuit and the "ultramicrometer" is coupled to a string galvanometer through a variable, decade condenser. This does away with the necessity of compensating for the "zero" plate current of the oscillator. In addition it furnishes a means of tuning the recording circuit.

Using a very light, tightly stretched string and a rather crude condenser microphone made from an antiquated telephone transmitter, we have been able to record sounds up to 650 double vibrations per second. Harmonics up to the 6th partial of spoken sounds showing a fundamental rate of about 100 are readily recorded. With a well constructed microphone the characteristics of the ordinary galvanometer string would be the limiting factor in recording sounds of high frequency. No attempt has been made as yet to determine the limits imposed by the string that we are using.

The microphone is placed directly on the chest wall. A hole drilled in the "mouthpiece" maintains atmospheric pressure in the vibrating column of air. The main source of "noise" seems to be the vibration of the elements of the electron tube. Mechanical shielding of the tube is necessary.

The heart sound records obtained resemble those made with Einthoven's "Saitenphonograph".[2] The 3rd heart sound appears in the records of all of the few subjects examined. So far we have had opportunity to obtain a record from only one case showing a heart murmur.

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[1] Dowling, J. J., *Phil. Mag.*, 1923, xlvi, 87.

4048

Extracellular Production of Toxin by Clostridium botulinum.

C. N. STARK, J. M. SHERMAN AND PAULINE STARK.

From Cornell University, Ithaca, New York.

It is well known that bacterial free filtrates containing the toxin of *Clostridium botulinum* increase in toxicity when mixed with certain substances such as normal blood serum and non-specific antitoxins. The observed increases have, as a rule, been relatively small (2 to 10 fold) and the observations have been variously interpreted by the several investigators. The possibility that the toxin might be produced extracellularly by the action of the enzymes of the organism on a suitable substrate has not been seriously entertained by the more prominent workers in this field; on the contrary, the belief is generally held that the toxin is produced only intracellularly.

From our own work with *Clostridium botulinum* (Type A) we have been led to the conclusion that the toxin is produced entirely intracellularly, or nearly so, in some media, while it may be produced both intracellularly and extracellularly in certain other media.

If a bacterial free filtrate of the botulinum organism is mixed with sterile skimmed milk and the mixture incubated at 37° C. until proteolysis ensues, a material increase in toxicity takes place. This is illustrated by the example given in Table I. In this experiment 1 part of the culture filtrate was mixed with 4 parts of sterile skimmed milk and the mixture incubated at 37° C. for 4 days. As a control, some of the same filtrate was incubated alone at the same temperature for the same period of time. After incubation, series of guinea pigs were inoculated with, (1) the incubated filtrate mixed with 4 parts of sterile physiological salt solution, (2) the incubated filtrate mixed with 4 parts of sterile skimmed milk within an hour previous to inoculation, and (3) the incubated filtrate-milk mixture referred to previously.

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[2] Einthoven and Hoogerwerf, *Pfluger's Archiv.*, 1924, cciv, 275.

TABLE I.
Action of Botulinum Filtrate upon Milk—4 to 1 Mixture.

cc. given	1	1/10	1/100	1/1000	1/5000
NaCl Solution and Filtrate (Mixed after incubation)	+	—	—	—	—
Milk and Filtrate (Mixed after incubation)	+	+	—	—	—
Milk and Filtrate Mixed (Incubated 4 days at 37° C.)	+	+	+	+	—

This result has been obtained again and again and we feel that these results together with certain other observations lend support to the view that the toxin may be produced extracellularly by the action of the enzymes of the organism on certain protein substrates. Similar results have been obtained with purified casein solutions in place of skimmed milk, and likewise when the filtrate is incubated with a suspension of sterile yeast cells. On the other hand, we have not succeeded in demonstrating a comparable increase in toxin when the filtrate is allowed to act upon peptone, ash-free gelatin, extract of fresh beef (in concentrations used in bacteriological media), and trypsin digested milk. While the trypsin digested milk yielded a greater increase in toxicity than the other substances which are listed as giving negative results, the increase was not comparable to that obtained from normal skimmed milk. This is suggestive.

That the increased toxicity obtained by the action of botulinum filtrate upon skimmed milk is due to an increase in the specific toxin is indicated by the fact that this toxicity was completely counteracted by a type A antitoxin procured from a biological supply house.

4049

Chronic Barbital Poisoning in the Rabbit.

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From the Departments of Pharmacology and Physiological Chemistry of Syracuse University.

Clinically chronic barbital poisoning has been observed repeatedly. On the other hand no observations upon the effects of repeated injections of this drug upon animals seem to have been reported. The desirability of comparing similarities of symptoms in man and in laboratory animals is obvious.

At the start of a 12 week period rabbits were injected daily with a dose of 0.03 gm. of soluble barbital which was gradually increased to reach 0.15 gm. at the end of the period.

At the end of the 12 week period there were no appreciable changes in weight, heart and respiratory rates, appearance of the skin and hair coat, in the amount and character of stools, whereas the urine output seemed to be slightly diminished. There was undoubtedly a marked vasodilatation in the animals as evidenced by the congestion of the ears. At the end of the period the blood sugar level was found to be normal.

The most outstanding effects produced were upon the central nervous system. There was a marked increase of irritability and restlessness. They developed a very peculiar disturbance in gait. The movements of the fore limbs were quite normal. The hind limbs, however, showed a very decided backward thrust, such as one might expect were the rabbits attempting forceful movements on a very slippery surface. In this connection it should be recalled that in chronic barbital poisoning in human subjects one frequently sees cerebellar ataxy. The motor phenomena described above resemble the "rebound" seen in man.

4050

The Effect of Subcutaneously Injected Epinephrin in Normal Human Subjects.

THEODORE KOPPÁNYI.

From the Department of Pharmacology, Syracuse University.

The conditions under which subcutaneously injected epinephrin gives a pressor effect in the dog, have been studied by Luckhardt and Koppányi,[1] who found that, when the site of injection has been massaged, there was a rise in blood pressure of from 15 to 180 mm. of Hg. following each massage. Lilienthal[2] used this method in the treatment of asthma and shock in man and obtained pressor responses upon massaging the injected area, for nearly 48 hours following the injection of 0.3 cc. of epinephrin 1:1000. The blood pressure elevations he obtained were comparatively slight (7 to 10 mm. of Hg.). In view of these observations it seemed desirable to investigate the action of subcutaneously injected epinephrin in normal human subjects.

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[1] Luckhardt and Koppányi, *Am. J. Physiol.*, 1927, lxxxi, 436.

[2] Lilienthal, *J. Am. Med. Assn.*, 1928, xc, 1192.

Six young healthy medical students were subjected to subcutaneous epinephrin injections (0.4 cc. of a 1:1000 solution). Before injection the normal systolic and diastolic blood pressure and the heart and respiratory rates were determined. From 10 to 15 minutes following the injection of epinephrin there was a rise in blood pressure of 30 to 50 mm. of Hg., a slight increase in the heart and respiratory rates without any massage. The injected area was blanched, the face pale, there was a slight muscular twitching in the arms and legs; and a thumping, palpitating heart was evident. The subjects felt slight head-ache, throbbing in the head, some nausea, the mouth was dry and there was in some cases subjective sensation of warmth, in others the hands and feet felt cold. Nervousness and general feeling of anxiety were evident in most subjects, whereas one subject appeared to be in a fighting mood.

The injected areas were massaged from 15 minutes to 48 hours following injections. In the course of the 48 hours the area was massaged about 25 times. On the whole, all the symptoms which appeared following epinephrin injection without massage, could be duplicated by massaging the injected area, *for about 48 hours*. They were, however, much less marked, the blood pressure rises for instance being seldom more than from 7 to 15 mm. of Hg. The rise was practically the same when one massaged the area 20 minutes or 20 hours following the injection. One subject developed constipation following the injection.

Comparing the results obtained in the dog and in man, it is evident that (a) there is a hemodynamic effect following the hypodermic injection of epinephrin in man even without massage, whereas no such effects occurred in the dog. Apparently in man epinephrin is more readily absorbed from the subcutaneous tissues, than in the dog. (b) Both in man and in dog the hypodermic epinephrine depot is not depleted for from 22 to 48 hours and may be utilized to produce hemodynamic effects upon massage. The blood pressure rises following massage are more marked in the dog than in man.

4051

Effect of Ash of Liver on Blood Regeneration in Pernicious Anemia.

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In connection with experiments conducted by Whipple, Robscheit-Robbins, Elden, and Sperry on the effect of ash of liver on blood regeneration in dogs,[1] observations were made of its effect in 3 cases of pernicious anemia.

The first of these (12986, Strong Memorial Hospital) was a woman, 55 years of age, with typical pernicious anemia. The hemoglobin was 20% (2.9 gm. per 100 cc.). The red cell count was 750,000. There was leucopenia, thrombocytopenia, marked aniso- and poikilocytosis, occasional normoblasts and stippled macrocytes. The reticulocytes constituted 1% of the erythrocytes. From February 8-25, 1928, the patient received 3 gm. of ash of beef liver daily, which represented 369 gm. of raw liver. The reticulocytes rose to 3% on the second day, 5 on the third, 6.5 on the fourth, 7 on the fifth and sixth days. The erythrocytes and hemoglobin remained unchanged. The leucocytes rose slightly on the sixth day. The patient was in a precarious condition due to the onset of a severe upper respiratory infection. She took little food of any kind, and the diet contained none of the foods known to be active in blood regeneration. With the onset of the intercurrent infection it was decided to give a transfusion of 500 cc. of citrated blood, which was done on the eighth day. Following this the reticulocytes decreased to 2% on the tenth day and remained at 1% throughout the remainder of the period. The hemoglobin rose to 32% and erythrocytes to 1.2 millions and remained at this level throughout the remaining period of 11 days. All evidences of regeneration were at a standstill after transfusion. On February 26th Minot's liver extract, No. 343, was given, equivalent to 300 gm. of liver daily. On the fifth day thereafter the usual signs of a remission appeared. The reticulocytes rose to a maximum of 12% on the seventh day. The patient subsequently had a complete remission.

The second patient (Strong Memorial Hospital No. 13857) was a woman of 60 years, with a typical pernicious anemia. The hemoglobin was 26%, erythrocytes 1.12 millions, leucopenia, aniso- and poikilocytosis, a few normoblasts, and punctate basophilia. The platelets were considerably reduced.

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[1] Robscheit-Robbins, Elden, Sperry, and Whipple, PROC. SOC. EXP. BIOL. AND MED., 1928, xxv, 416.

The patient was first given the whole ash of liver in doses amounting to from 3.0 to 4.5 gm. per diem, representing 369 to 387 gm. raw liver. Subsequently the ash was treated with hydrochloric acid to dissolve it, the acid was neutralized, and the salts evaporated to dryness, this was given in equivalent doses. Finally, Minot's liver extract 343 was given in equivalence of 300 gm. liver.

The course of events is best shown in the graphical chart, Fig. 1.

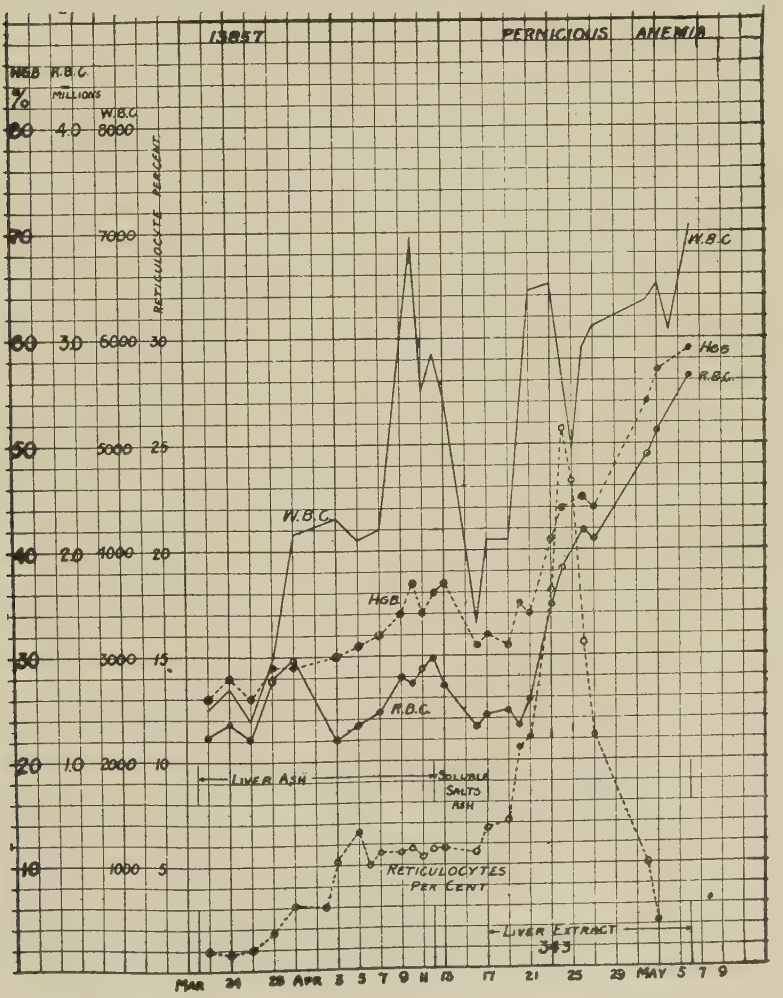

FIG. 1.

Effect of liver ash compared with Minot's Liver Extract No. 343 in pernicious anemia.

During the period of 22 days in which liver ash was given, many of the preliminary phenomena of a remission were observed. The hemoglobin rose from 26 to 37%, the erythrocytes fluctuated from 1.2 to 1.5 millions. The leucocytes increased from 2500 to 7000. The reticulocytes began to increase on the 7th day and reached a maximum of 6.5% on the 17th day, remaining at about that level until further elevated by the administration of the liver extract.

The signs of beginning regeneration just enumerated began to diminish as soon as the soluble salts of the liver ash were given. After a few days it was determined to discontinue the ash experiment. When Minot's liver extract was given a true remission of the disease began.

A third patient with pernicious anemia received the soluble salts of the liver ash for a period of a week. There was no evidence of any activity of marrow tissue observed, either in the total blood count and hemoglobin and leucocytes or in the percentage of reticulocytes.

These results are reported as a supplement to the experiments of Whipple and Robscheit-Robbins on the effects of liver ash and inorganic substances on the blood regeneration of dogs made chronically anemic by repeated bleedings.

Conclusions: 1. The administration of the ash of liver to 2 patients with typical pernicious anemia resulted in the appearance of some of the preliminary phenomena of a remission, in particular an increase in the percentage of reticulocytes. In neither case did a true remission occur until Minot's liver extract 343 was given.

2. The substance responsible for the above was apparently lost or inactivated by dissolving the ash in hydrochloric acid, neutralizing with NaOH, and evaporating the salts to dryness.

4052

Blood Regeneration in Severe Experimental Anemia. Influence of Inorganic Elements.

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W. M. SPERRY.

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School of Medicine and Dentistry.*

We have recently reported in these Proceedings[1] a rather startling reaction to the inorganic ash of liver, kidney and apricots. This ash incorporated in a standard anemia diet[2] given to dogs kept constantly anemic by bleeding will effect a notable increase in blood hemoglobin production above control periods. This may amount to 30 to 50 gm. hemoglobin per 2-week period.

We have made various analyses of these ashes and from such data have made various synthetic ash compounds, but such synthetic mixtures so far have not proved to be potent. These experimental data will be published in due time.

We wish to report briefly our findings when these dogs are given various simple salts added to the standard ration. It is apparent that in the doses given iron is more potent than either copper or zinc.

TABLE I.

Hemoglobin Regeneration and Inorganic Elements.

Minerals	Amount per day	Hemoglobin produced per 2 weeks	Number of experiments
	mg.	gm.	
*Bread control		2— 5	
Iron (chloride)	25	0—10	6
Iron (citrate)	60	10—70	2
Iron (citrate)	300	40—70	4
Copper (tartrate)	40	0	2
Copper (sulfate)	65	13	2
Copper (tartrate) + iron (chloride)	40 + 140	27	1
Copper (tartrate) + iron (chloride)	20 + 36	27	1
Copper (tartrate) + iron (chloride)	40 + 70	60	1
Zinc (chloride)	11	20	2
Zinc (chloride) + copper (tartrate)	24 + 40	9	1
Manganese (peptonate)	110	0	1
Aluminum (sodium sulfate)	38	0	2
Arsenic (potassium arsenite)	2	0	2
Antimony (chloride)	9	0	1
Iodide (sodium)	420	0	1

* Standard bread ration per 300 gm. contains 18 mg. iron.

Values of copper, iron, zinc, aluminum, arsenic, antimony and iodine are given in mg. of the element. The manganese is given in mg. of the peptonate.

These observations dealing with copper salts are of considerable interest when contrasted with the recent reports of Hart, Steenbock, Waddell and Elvehjem,[3] who report a distinctly favorable reaction to copper salts and a negative reaction to iron salts. These distinct differences between our experiments and those of the Wis-

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[1] Robscheit-Robbins, F. S., Elden, C. A., Sperry, W. M., and Whipple, G. H., PROC. SOC. EXP. BIOL. AND MED., 1928, xxv, 416.

[2] Whipple, G. H., and Robscheit-Robbins, F. S., *Am. J. Physiol.*, 1925, lxxii, 395.

[3] Hart, E. B., Steenbock, H., Waddell, J., and Elvehjem, C. A., *J. Biol. Chem.*, lxxvii, 797.

consin investigators must be explained on the basis of animal differences or anemia differences. They use rats made anemic by faulty diets and we use dogs made anemic by constant bleeding to a standard anemia level.

Early in our anemia experiments (1923) Robscheit-Robbins and Whipple observed that an excess of a salt mixture (McCollum and Simmonds[4] minus iron) caused a distinct increase in hemoglobin production over control periods. The control bread ration contained these same salts but a large excess added would cause an increased hemoglobin output. It could not be that these salts were incorporated in the hemoglobin molecule, so this reaction might be called "catalytic." We feel that these large doses of iron reported here, which are probably 10 times or more in excess of the body needs, cause a similar *salt reaction* of "catalytic" nature. There must be a readjustment of the internal protein metabolism so that much more hemoglobin is produced, there being an excess of iron at all times.

The doses of copper, zinc and other metals are close to the toxic dosage. We intend to extend these observations, using a variety of dosage and combinations of various salts. This is a progress report.

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[4] McCollum, E. V., and Simmonds, Nina. *J. Biol. Chem.*, 1918, xxxiii, 63.

Wisconsin Branch.

University of Wisconsin, May 9, 1928.

4053

Introduction of Iodized Oil into Respiratory Tract of Dog.

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While the introduction of substances opaque to the X-ray was begun as early as 1905 it was not until the work of Sicard and Forrestier[1] in 1921 that the practice became general. They used a chemical combination of iodine and poppy-seed oil which is called lipiodol. This is now in general use in diagnosis and in limited use in therapy. Our immediate interest was whether it injured a normal healthy lung.

During the past 2 years we gave dogs repeated doses of lipiodol. During the year 1926-27 most of the work was done by M. I. Smedal and P. A. Duehr.

In one group the dogs were given 2 cc. per kilo body weight and repeated when their urine became iodine free. This period varied from 23 to 67 days. The first 4 dogs belong to this group. In the remaining dogs the treatment was empirical as is often the case in the clinic. Five small dogs averaging about 8 kilos were selected and the oil introduced at convenient periods.

In both groups the several methods of administering the oil were used. Errors as well as hits are recorded so that one may have an idea of how much oil each dog received.

No. 1 received 10 cc. in the right lung Jan. 1; 10 cc. in the pretracheal fascia Feb. 17; autopsied April 26.

No. 2 received 10 cc. in both lungs Feb. 26; 10 cc. in the stomach March 26; 10 cc. in both lungs April 2; autopsied May 3.

No. 3 received 7 cc. in both lungs Feb. 17—most of this was soon coughed up and swallowed; 7 cc. in both lungs Feb. 26; 12 cc. in both lungs April 23; autopsied May 4.

No. 4 received 12 cc. in both lungs April 23; autopsied May 4.

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[1] Forrestier, J., *Radiology*, 1926, vi, 303.

No. 5 received 5 cc. in the left lung Dec. 20; 5 cc. in both lungs Jan. 3 and 21; 8 cc. in the pretracheal fascia Feb. 17; 8 cc. in the right lung and stomach March 19; 9 cc. in the left lung March 26; autopsied April 27.

No. 6 received 10 cc. in the right lung Aug. 23; 10 cc. in the stomach Sept. 8, 15, 27; 10 cc. in the left lung Oct. 8; 10 cc. in the right lung Oct. 22 and Nov. 8; 10 cc. in both lungs Nov. 22; 10 cc. in the right lung Dec. 5; autopsied March 16.

No. 7 received 10 cc. in the stomach Aug. 27; 10 cc. in both lungs Sept. 8; 10 cc. in the right lung Sept. 15; 10 cc. in the stomach Sept. 27; 10 cc. in the right lung Oct. 8, 22, Nov. 8; 10 cc. in both lungs Nov. 22; 10 cc. in the right lung Dec. 6; autopsied March 15.

No. 8 received 10 cc. in the right lung Aug. 23; 10 cc. in both lungs Sept. 8, 15; 10 cc. in the right lung Sept. 27; 10 cc. in the left lung Oct. 8; 10 cc. in both lungs Oct. 22 and Nov. 8; 10 cc. in the right lung Nov. 22; died of hemorrhagic diarrhea Dec. 12.

No. 9 received 5 cc. in both lungs Aug. 23; 10 cc. in both lungs Sept. 8; 10 cc. in the stomach Sept. 15; 10 cc. in both lungs Sept. 27; 10 cc. in the right lung Oct. 8, 22; 10 cc. in the left lung Nov. 8; 10 cc. in both lungs Nov. 22 and Dec. 6; autopsied March 5.

In the first group iodine tests of the urine were made regularly as were also differential blood counts. While these latter were of interest to us we do not feel that they were accurate enough to report. While an occasional animal lost in weight their health on the whole was excellent. The greatest amount of oil given any one dog was 75 cc.; the longest period that any dog was under observation was 205 days.

At autopsy the lungs were studied in detail and in this we had the cooperation of various members of the Department of Pathology. Some attention was given to the other organs, especially the kidneys and spleen. The gross findings as a whole were negative. The microscopic examinations in some cases showed a small amount of fibrosis and in occasional areas toward the periphery there was a chronic passive congestion.

Pinkerton[2] recently reporting a series of observations on the use of various oils in diagnosis found that iodized poppy seed oil produced practically no reaction. He, of course, was using but one dose.

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[2] Pinkerton, A., *Arch. of Path.*, 1928, v.

4054

Dormancy of Spores of Cl. Acetobutylicum and Cl. Pasteurianum.

ELIZABETH MC COY AND E. G. HASTINGS.

From the Department of Agricultural Bacteriology, University of Wisconsin.

The time required for the germination of anaerobic spores following single cell isolation is extremely variable, as may be seen from the records of 2 strictly anaerobic bacteria, *Cl. acetobutylicum* and *Cl. Pasteurianum.* Spores were picked with the modified Chambers micromanipulator and were immediately transferred to suitable culture media, beef-peptone-glucose agar, corn mash, milk, Hall's brain mash, or Speakman's synthetic medium. Sterile vaseline was layered onto the medium to maintain anaerobic conditions and to prevent evaporation during long incubation. From 100 isolations of *Cl. acetobutylicum* and 14 of *Cl. Pasteurianum* the 6 cultures as given in the table were obtained.

TABLE I.
The Germination Time of Single Anaerobic Spores.

Culture	Medium	Time before germination
Cl. acetobutylicum		days
1. No. 105	Beef-peptone-glucose-agar	11
2. No. 105	Milk	117
3. No. 105	Milk	222
4. No. 70	Brain mash	19
5. No. 70	Corn mash	21 + (*)
Cl. Pasteurianum		
1. No. 5	Synthetic	72

(*) Germination between the 21st and 25th day.

Why should a spore lie dormant for 222 days or, for that matter, for 11 days before germination? Conditions of temperature, available food, and anaerobiosis were favorable during the entire period. As far as we know there was no change which might have acted as the final stimulus to germination. It was suggested that perhaps a spore, like a seed, needed a period of ripening after being set free from its mother sporangium. However, a review of the ages of spores when picked does not bear this out. No. 70 (4) with a dormancy of only 19 days came from a free spore in an agar colony 96 hours old while No. 105 (3) with the extreme dormancy of 222 days came from a stock culture in corn mash 1 year old.

Even the extreme germination time in the table is far shorter than the extreme recently reported by Dickson.[1] He found growth in a thermal death point experiment on *Cl. botulinum* 72 months after heating. However, his *Cl. botulinum* spores may have been injured by heating while those of *Cl. acetobutylicum* and *Cl. Pasteurianum* picked directly from stock cultures should be of unimpaired vitality.

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[1] Dickson, E. C., PROC. SOC. EXP. BIOL. AND MED., 1928, xxv, 426.

Why should some single spores, always a low percentage of those picked, germinate in the end. Shall we believe that the others were not viable when picked, died during incubation, or are still alive and dormant? We have no way of answering, but what we do know of dormancy in single spore isolations should make us very cautious about making definite statements that a culture is killed by a certain treatment or that a substance is free from anaerobic spores.

4055

Inhibition of Ovulation and Associated Histological Changes.*

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From the Department of Zoology, University of Wisconsin.

The idea that the corpus luteum is responsible for the inhibition of ovulation seems to have been first elaborated by Beard[1] and by Prenant.[2] The experimental proof of the inhibitory action of the corpus luteum has been attacked in many different ways. The two most general methods have been based on anatomical and physiological modifications of the reproductive tract, correlated with the presence or absence of a functional corpus luteum, and, changes produced by the injection of extracts of lutein tissue. Corner and Hurni[3] reported negative results in an attempt to inhibit ovulation by injecting corpus luteum extracts in normal white rats. Loeb[4] failed to obtain consistent positive results in the guinea pig, while Papanicalaou[5] recently reported inhibition of ovulation in the same animal. Pearl and Surface[6] were able to stop hens from laying by injections of water extracts of a dried commercial preparation.

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* This work has been assisted by grants from the Committee for Research on Problems of Sex, of the National Research Council.

[1] Beard, J., Jena, 1897.

[2] Prenant, A., *Rev. Med. de l'Est.*, 1898, xxx, 385.

[3] Corner, G. W., and Hurni, F. H., *Am. J. Phys.*, 1918, xlvi, 483.

[4] Loeb, L., *Biol. Bull.*, 1914, xxvii, 1.

[5] Papanicolaou, G. N., *J. Am. Med. Assn.*, 1926, lxxxvi, 1422.

[6] Pearl, R., and Surface, F. M., *J. Biol. Chem.*, 1914, xix, 236.

Kennedy[7] described positive results on the rabbit for extracts made from a desiccated commercial preparation which were injected for a period of time before mating, resulting in the inhibition of ovulation. Parkes and Bellerby[8] reported inhibition of ovulation in mice by injections of an emulsion of an ether extract of the corpus luteum of the cow. They noted that not all of their extracts were potent, and that those that were soon deteriorated. Many different kinds of extracts have been employed by various investigators but the results obtained through their use are so contradictory that they cannot be discussed in this brief report.

An acid alcohol extract of the fresh corpus luteum of the sow has been prepared in this laboratory and refined to the extent that very little protein remains. This preparation is capable of sensitizing the uterus of spayed rats and guinea pigs so that placentomata may be produced (Weichert).[9] It will relax the pubic ligaments of virgin guinea pigs in oestrum (Hisaw)[10]; and will inhibit ovulation and oestrum in the normal female albino rat. Inhibition of oestrum was best effected by subcutaneous injections of an amount equivalent to 3 gm. of fresh tissue given every 4 or 5 hours from the beginning of oestrum until the experiment was ended. Rats injected in this manner did not come into oestrum for 6 to 12 days, the length of time for which ovulation was inhibited depending upon the amount of the extract injected. Attempts are now being made to inhibit ovulation for a greater period and to determine at what stage of the dioestrous interval injections may be most effective.

A histological study was made of the ovaries, uterus and vagina of the animals in which ovulation had been inhibited. The ovaries of these animals showed many involuting corpora lutea with the presence of large mature follicles in cases where oestrum had been inhibited for 12 days. The uterus presented the picture found in pregnant and pseudopregnant rats. The outer layers of the vaginal mucosa were composed of tall, columnar, vacuolated cells, the amount of vacuolation and the growth of the vaginal mucosa being directly proportional to the length of time for which the ovulation had been inhibited. Long and Evans[11] described similar histological pictures in the reproductive tract of the albino rats during pregnancy and pseudopregnancy. The only difference between the normal conditions as reported by these authors and that produced by the injection of corpus luteum extracts is one of degree. The height of the vaginal mucosa and the vacuolation of the same was greater, when ovulation had been inhibited by extracts of the corpus luteum, than is normally found during pregnancy and pseudopregnancy.

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[7] Kennedy, W. P., *Quart. J. Exp. Phys.*, 1924, xv, 103.

[8] Parkes, A. S., and Bellerby, C. W., *J. of Phys.*, lxiv, 232.

[9] Weichert, C. K., PROC. SOC. EXP. BIOL. AND MED., 1928, xxv, 490.

[10] Hisaw, F. L., reported at the meeting of the A. A. A. S. at Nashville, Tenn., 1927.

[11] Long, J. A., and Evans, H. M., Memoirs of the University of California, vi, 1922.

In order to determine whether the corpus luteum, the follicular hormone or the interaction of both of these substances was responsible for the histological condition just described, these hormones were used separately and in combination on castrated female rats. The results of this study demonstrated that neither the corpus luteum nor the follicular hormone alone was responsible for the picture of pregnancy as found in the vaginas of normal rats, in which ovulation had been inhibited by injection of corpus luteum extracts. The experiment did show, however, that the changes occurring in the vaginas of such animals were due to the action of first, the follicular hormone, and, second, the subsequent effect of the corpus luteum hormone. The data at hand seem to indicate that the proliferation of the cells of the vaginal mucosa is produced by the follicular hormone while the corpus luteum hormone is responsible for the vacuolation of these cells.

These results agree with the physiological relationship of these 2 hormones, described by Hisaw,[10] who found that the pelvic ligaments of the virgin female guinea pig must first come under the influence of the follicular hormone before the corpus luteum hormone could produce relaxation of the symphysis pubis. A similar relationship was described by Weichert[9] for the production of placentomata in castrated female rats and guinea pigs. Thus it seems that the inhibition of oestrum and ovulation is due to the corpus luteum hormone alone while the histological changes produced in the uterus and vagina are brought about through a cooperation of the follicular and the corpus luteum hormones in which the former must act before the latter can function.

4056

Sympathectomy in the Goat.

O. A. MORTENSEN, K. F. FRIEDBACHER AND R. H. QUADE.
(Introduced by W. E. Sullivan.)

From the Department of Anatomy, University of Wisconsin.

Interest in the relation between the sympathetic nervous system and the striated limb musculature was revived by the experiments of Hunter and Royle.[1] They described a loss of plastic tonus in the hind limb of the goat and in the wing of the fowl following the severence of the sympathetic connections to these parts. By the loss of plastic tonus they meant the loss of an intrinsic muscular supporting mechanism controlled by the sympathetic nervous system which functioned to maintain the position of the limb after the ordinary somatically innervated fibers had ceased contracting. Later experiments by other workers who used the dog and cat chiefly, failed to confirm these observations. We are reporting the results of unilateral right or left lumbar sympathectomy performed on 7 young normal goats.

Our general procedure was (1) examination of the normal animal, (2) left or right lumbar sympathectomy, (3) comparison of normal and operated sides following sympathectomy, (4) decerebration, (5) comparison of normal and sympathectomized limb during decerebrate rigidity.

The chief purpose of the normal examination was to elicit any evidences of right or left leggedness. We observed the movements of walking, running, and jumping and also examined the postural reflexes as they have been described by Magnus.[2] This is done by placing the animal on its back in a cradle and noting the changes in the position and tone of the limbs after rotation of the head on the neck. The results of the normal examination indicated (1) right-leggedness in one animal which persisted throughout the subsequent procedures, (2) the postural reflexes in the normal goat are identical to those in the animals Magnus has worked with.

We found the lateral retro peritoneal approach to the lumbar chain to be the most satisfactory. Autopsy indicated that we succeeded in removing the 2nd to the 5th, inclusive, lumbar ganglia in the majority of instances. The wounds healed readily; the recovery from this procedure was uneventful.

Within 5 to 15 minutes after the chain had been divided there was a palpable difference in temperature between the normal and the operated side; the operated side felt distinctly warmer. We did not follow the blood vessel changes closely but we incidentally noted this change in temperature 47 days after operation in one animal. Ten days to 2 weeks after sympathectomy we repeated the procedure of the normal examination and recorded the latent period of the knee reflex. By these methods we were unable to find any constant differences between the normal and the operated sides. Slight differences in position and tonus between the 2 sides would on one occasion indicate a decrease in tone on the operated side and during a repeated examination the same limb would often show a slight increase in tone. The position of the animal is a very important factor and we feel that the changes in tonus we observed could be explained by deviation from the standard midline position. The majority of the reflexes indicate a slight increase in the latent period following sympathectomy but the difference was slight, variable and not outside the limits of the experimental error.

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[1] Hunter, J. I., *Med. J. Australia,* 1924, lxxxvi.

[2] Magnus, R., *Körperstellung,* 1924.

Decerebration was accomplished by removal of the posterior part of the bony vault and cerebral hemisphere. The midbrain was exposed and sectioned with a blunt dissector just posterior to the superior colliculus. We are very grateful to Drs. Gale and Hinsey and to Mr. William Kaplan for their help with this procedure. Five of the 7 animals were decerebrated successfully.

About 20 minutes after the section was made the wink and knee reflexes returned; the breathing and pulse rate became regular and steady and we considered the animal ready for study. Again we were unable to demonstrate any constant differences between the normal and sympathectomized limb by the methods already referred to. In some animals there was a temporary difference in the degree of rigidity which at first seemed significant but which later proved to be due to the fact that the animal had been lying on the affected side during the operation. Occasionally we observed changes in tone while the animal was in a certain position and then found by changing the position the difference in the tone disappeared. The postural reflexes are present and unaltered by decerebration; the latent period of the knee reflex showed no change following decerebration. We roughly measured the degree of rigidity by suspending the animal in a frame and resting the limb on a kitchen scale following the method of Ranson and Hinsey.[3] By this method of measurement the degree of rigidity seemed to be unaltered by the previous sympathectomy.

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[3] Ranson, S. W., and Hinsey, J. C., *J. Comp. Neur.*, 1926, xlii, 69.

As a result of our experiment we are unable to demonstrate any changes in tone in the hind limb of the goat following the removal of the 2nd to the 5th lumbar sympathetic ganglia.

4057

Transplantation of Placental Tissue.

MERLYN G. HENRY and H. W. MOSSMAN. (Introduced by W. E. Sullivan.)

From the Anatomical Laboratory, University of Wisconsin.

Frankl,[1] using mice, showed that "a successful transplantation of a placenta (fetal portion) on a pregnant animal causes persistence of colostrum secretion" beyond the normal period following the birth of the young. Unless the transplants were removed the litters born to engrafted mothers died "evidently from starvation." Stimson[2] and others report in women with retained placenta, suppression of the secretion of true milk. Our first attempts, without knowledge of these results, were made to obtain living grafts of the fetal or trophoblastic portion of rabbit and rat placentae. In all cases neither gross nor microscopic examination gave evidence of growth after implantation. Since Frankl's results have been used in interpretating the relation of the placental hormones to lactation, and because our experiments, which extended over a period of about a year, have been discontinued, it seems desirable to report our work briefly.

We used trophoblastic tissue (fetal placenta) from rabbits varying in stages of pregnancy from 2 weeks to near full-term, and from rats during mid and later pregnancy. Thin slices of tissue were implanted subcutaneously and intramuscularly, and intraperitoneally in both rats and rabbits. Emulsions of placental cells in Locke's solution were injected into the ear vein of rabbits, and subcutaneously, intramuscularly, and intraperitoneally into both rabbits and rats. Host animals have been, the female from whom the tissues were taken, other females both young and mature, males, and in the case of the rat, also young, about one-fourth grown. Extirpation and implantation in the case of both rabbits and rats was done aseptically under chloral-urethane anesthesia administered by stomach-tube and supplemented by ether. Animals were killed and examined at varying times from 3 days to one month after grafting. Microscopic examinations were made only in cases where gross findings indicated some chance of viability of the graft.

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[1] Frankl, Oskar, *Am. J. Obstet. and Gynec.*, 1923, vi, 399.

[2] Stimson, C. M., *Am. J. Obstet. and Gynec.*, 1922, iv, 413.

The following details of our technique should be mentioned. Placental emulsions were made either by squeezing the tissue through sterile gauze into Locke's solution maintained by a water-bath at approximately body temperature, or by quickly cutting a small bit of tissue lying on gauze into a pulp by a few rapid strokes with a razor and then transferring it to Locke's. This emulsion was taken up by a warm Luer syringe through a 20 gauge needle and injected immediately. In a few cases small amounts of tissue were injected successfully without dilution. The time from the removal of the tissue to the injection was not more than 2 or 3 minutes. After injecting, some of the emulsion remaining in the syringe was forced through the needle onto a slide and a smear made. These were dried, fixed in formalin or Bouin's, and stained with hematoxylin and eosin as a check on the actual nature of the material injected They showed scattered maternal and fetal blood cells and trophoblastic tissue ranging from cells with one nucleus to small masses containing dozens of nuclei. For grafts small pieces of fetal placenta between one and 2 millimeters in thickness were made with a razor, the blood and serum removed with gauze moistened in Locke's solution, and the piece laid in the previously prepared bed within less than 2 minutes from the time of extirpation. The beds were always made "dry", *i. e.,* free from oozing, before the graft was placed. Excess pressure and tension upon the graft after implantation was guarded against by so arranging the position of the pocket that the sutures in the fascia and skin did not fall directly over it. When microscopic sections of the grafts were made the paraffin method was used, sections were cut 7 to 10 micra, and stained in hematoxylin and eosin.

While we were not experienced in the technique of transplanting we feel that by following the relatively simple principles of asepsis and grafting as given by Neuhof[3] and others, our methods were certainly good enough to give us reason to expect some viable transplants, unless these are unusually difficult to obtain from trophoblastic tissue. Only a few of our cases became infected. Frankl states that one-third of his cases became infected. Many so far uncontrolled factors may influence the behavior of placental transplants, such as the age of the placenta and the stage in the oestrous or pregnancy cycle of the recipient. We believe that more carefully controlled experiments will have to be made before it can be said with any certainty that normal trophoblastic tissue will or will not grow as a graft outside the uterine mucosa.

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[3] Neuhof, Harold, "Transplantation of Tissues," 1923.

Since submission of this manuscript Prof. Frankl in a personal communication has made clear that grafts which he called successful lived until the time of sectioning without showing necrotic changes, but did not show actual growth.

4058

Reaction of White Blood Cells to Specific Precipitate.

H. W. CROMWELL. (Introduced by Paul F. Clark.)

From the Laboratory of Medical Bacteriology, University of Wisconsin.

When fresh citrated normal rabbit blood is mixed with the specific precipitate obtained by combination of antigen with antibody, the polymorphonuclears, the large mononuclears, and apparently, also the large lymphocytes become extensively vacuolated. The cells are often so crowded with vacuoles that they appear swollen and the nuclei are pushed to one side. Similar vacuolation though not so extensive, is also seen in the peripheral blood of a highly immune animal about 2 hours after intravenous injection of the specific protein. The reaction apparently occurs regardless of the antigenic protein used since it has been found with the specific precipitates of crystalline egg albumin, excelsin, human ascitic fluid, human seminal fluid, and horse hemoglobin. When the normal blood is mixed with the antigen only, a little vacuolation occurs occasionally in the mononuclear types of cells, the polymorphonuclears remaining entirely unaffected. No vacuolation occurs at all when the blood is mixed with the supernatant serum after removal of the specific precipitate by centrifugation.

It is considered that the vacuoles probably do not represent degeneration processes because: (1) although the changes are best seen after 1 or 2 hours, they are well marked within 15 to 30 minutes; (2) the cell morphology remains distinct, the vacuoles clear-cut and the nucleus and cytoplasm retain their normal reactions to Wright's stain. It is suggested that these changes may be due to the phagocytosis of the specific precipitate.

Southern Branch.

Tulane University, May 22, 1928.

4059

Difficulty in Cultivation of Endamoeba Histolytica.

M. W. MILLER. (Introduced by Henry Laurens.)

From the Department of Medicine, Tulane University School of Medicine.

Reports describing the ease with which a number of workers[1] have cultivated *E. histolytica* have led me to attempt its culture.

Following the method described by Boeck and Drbohlav,[2] material obtained from 19 patients with proved *E. histolytica* infection was inoculated into their L. E. S. medium. The material obtained from 15 patients showed vegetative forms of ameba only; from 2 patients encysted forms of ameba only; and from 2 patients both encysted and vegetative forms of ameba. The results of these inoculations are embodied in the following table:

TABLE I.

Material used for inoculation	No. of patients	Growth of ameba	Life of culture in days	Successful subcultures
Inoculum containing vegetative forms of amoeba only.				
Bloody mucoid stools	15	0	0	0
Scrapings from ulcers	12	2	1	0
Bloody mucoid stools after 24 hours in ice box	4	0	0	0
Tissues removed at necropsy	1	0	0	0
Tissues removed at necropsy treated with alkali	1	0	0	0
Tissues removed at necropsy treated with acid	1	0	0	0
Tissues removed at biopsy	1	0	0	0
Inoculum containing vegetative and encysted forms.				
Bloody mucoid stools	2	0	0	0
Inoculum containing encysted forms only.				
Semi-solid feces	2	0	0	0
Concentrated fecal washings	2	1	1	0

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[1] Craig, C. F., and St. John, J. H., *Am. J. Trop. Med.*, 1927, vii, 39.

[2] Boeck, W. C., and Drbohlav, *Am. J. Hygiene*, 1925, v, 371.

Treatment of the ameba containing material with refrigeration, with acid, and with alkali, was done in an attempt to enhance their resistance and to cause them to encyst. In the few instances tried, the treatment proved to be of no value.

Five tubes of media as a minimum were inoculated in each attempt to cultivate ameba from a given patient. Where amebic growth occurred, it was found in at least 2 of the tubes inoculated.

The initial pH of the media varies between 6.8 and 7. The average pH at the end of 24 hours incubation from the cultures from 5 patients was 6.4; at 48 hours 5.6. A pH value of less than 5.4 was never encountered. Protozoal life could not be demonstrated at a pH of less than 6.2. Reinforcement of the buffer value of the serum by the addition of dibasic sodium phosphate did not materially affect the hydrogen ion concentration. The addition of washed human red cells showed no effect on the growth of the ameba or the reaction of the media. The addition of calculated amounts of alkali at short intervals, in the cultures from 2 patients maintained the pH only temporarily but did not affect the growth of the ameba.

Simultaneous inoculation of media with infected material and an alkali producing organism (probably *B. alkaligines*) obtained from the culture of stools in the cultures from 4 patients resulted in a less rapid swing of the pH to the acid side and maintained as a final acid figure the pH 6.2.

The small series of cases above reported demonstrates the difficulty encountered in the cultivation of *E. histolytica*. Some improvement, however, is noted in Dobell's[3] modification of Boeck and Drbholav's medium, as there is at present an undoubted culture of *E. histolytica* growing in the laboratory, on the latter media, through 4 successive subcultures. Attempts to grow this organism on the first media used have been futile.

4060

Surgical Relief of Pericardial Adhesions: An Experimental Study.

ALTON OCHSNER AND GEORGE R. HERRMANN.

From the Departments of Surgery and Medicine, School of Medicine, Tulane University.

The operative procedures employed today to relieve symptoms produced by pericardial adhesions consist of (1) removing the extra pericardial adhesions extending between the pericardium and the thoracic wall (cardiolysis) and (2) extirpation of the pericardium (decortication) in those cases in which there is considerable fibrous contraction of the pericardium. It is self evident that both of these procedures are largely palliative and have been performed in patients with marked cardiac damage.

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[3] Personal communication from Dr. F. M. Johns.

Delorme[3] advocated the division of the intrapericardial adhesions, but, because of the invariable recurrence of the adhesions, this operation was soon abandoned. Believing that the re-formation of pericardial adhesions might be prevented following their division as peritoneal adhesions by the use of digestants,[4] the following experiments were performed:

Sixty-five dogs were used. Roentgenograms and electrocardiograms in 3 positions (back, left and right) were taken before and after each operation and immediately before sacrificing the animal. Careful clinical and radiographic observations were made pre and post operatively. As a preliminary operation a pericarditis was produced by introducing irritating inorganic and organic substances into the pericardial cavity, as performed by Herrmann and Musser.[5] Pericardial adhesions, usually causing a complete synechia of the pericardial cavity, resulted in all animals.

After varying periods of time, a 2nd pericardotomy was performed, and the pericardial adhesions were divided. In one series a vegetable digestant of the papain group was introduced into the pericardial cavity, following the division of the adhesions, in order to prevent their re-formation. In one control series physiological saline solution, and in another 2nd control series nothing, was introduced into the pericardial cavity.

Of the 65 animals many were lost early in the series, because of faulty technic. Many died as a result of barbitol anesthesia. In the control animals in which, following the division of the pericardial adhesions, either nothing or physiological saline solution was added to the pericardial cavity, adhesions invariably re-formed.

Due to sucking back of water from the water pump while steril-

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[1] Brauer, L., *Nat. Hist. Verein. Heidelberg,* May 13, 1921; *Abs. Muench. Med., Wchschr.,* 1902, 1072.

[2] Parlevechhio, *Pericardectomia sperimentale e sue possibli applicazioni terapeutiche Policlinico sez chirurg,* 1908, xv, 8.

[3] Delorme, *Bull. et mem. de la Soc. de Chir.,* 827, 898.

[4] Ochner, Alton, and Mason, Frank, PROC. SOC. EXP. BIOL. AND MED., 1928, xxv, 524.

[5] Herrmann, George R., and Musser, John H., PROC. SOC. EXP. BIOL. AND MED., 1928, xxv, 314.

izing the digestant solution, which was done by passing it through a Berkefeldt filter, the digestant solution became contaminated in 3 instances. Of the 10 animals in which, in addition to the separation of the adhesions, the digestant solution was added to the pericardial cavity, no adhesions re-formed in 3. The other 7 showed evidence of extensive pleural infection, and in 3 the digestant solution contained organisms at the time of its introduction into the pericardial cavity. It has been previously shown that the digestant solution will not prevent adhesions in the presence of infection.

Evidence is submitted that the re-formation of experimentally produced pericardial adhesions may, following their division, be prevented following digestant solutions.

4061

Some Observations on Experimental Arteriovenous Aneurysm.

I. MIMS GAGE AND GEORGE R. HERRMANN.

From the Departments of Surgery and Medicine, Tulane University.

Arteriovenous aneurysm experimentally produced in the dog has been the subject of many studies, but we feel that there are still some mooted questions to be elucidated and many interesting facts to be established. Clinical experiences, under the stimulating influence of Professor Rudolph Matas, with his intense enthusiasm in this subject, have prompted our experiments. The earlier experiments were disappointing because of the almost invariable thrombosis of the vessels, but one of us (Gage) has now perfected the technique to the point where a functioning arteriovenous aneurysm always results. A technique of the operation, roughly comparable to that of side-to-side intestinal anastomosia has yielded uniformly successful fistulae. The common carotid artery and external jugular vein were the chief vessels in which anastomoses were accomplished.

Arteriovenous aneurysm has been successfully produced in 8 dogs. The clinical observations on these, 4 of which have died, will form the basis of this report. The lesions have been present in the dogs that have been sacrificed for 4, 40, 80, and 140 days. Four animals have now had functioning fistulae for 120 days, and are apparently unaffected by the presence of the lesion.

Control electrocardiograms were taken with the dogs in 3 standard positions, on the back, on the left, and on the right side. Control teleoroentgenograms were made, and the phase of respiration noted. The animals were operated under complete barbitol and ether anesthesia.

Several interesting observations presented themselves to us immediately after removing the clamps from the completed arteriovenous fistula. There was bleeding from the suture holes, which stopped within 2 minutes. Dilatation of proximal and distal segments of the vein appeared, most marked in proximal segment. Whirling eddies were noted in the vein, with the point of maximum intensity 1 to 1.5 cm. distal to the fistulous opening. An increase in diameter and stretching of the proximal artery was uniformly present. The intensity of the thrill and bruit is seen to be dependent upon the size of the vein, the size of the fistula, and the mass of the blood column passing unobstructed past the fistulous opening directly back to the heart.

In some instances where there is complete obstruction to the proximal segment of the vein, although the arterial blood could be seen passing into the distal segment of the vein, producing whirling eddies, there was neither a thrill nor a bruit present. Where no obstruction persisted the thrill extended several centimeters distally and proximally along the vein.

Clinically the thrills were felt for several centimeters along the vessels with, however, a maximal impulse about a centimeter distal to the actual orifice of the fistulae. The Branham phenomena, a sharp drop in the pulse rate and a slight rise in the systolic and diastolic blood pressures, were present in all of the animals.

Fluoroscopic studies confirmed previous observations of immediate and conspicuous cardiac dilatation upon first opening the fistulae. Teleoroentgenograms subsequently taken in the same phase of respiration that the control was taken uniformly and regularly showed increasing enlargement of the cardiac shadow at monthly intervals, even though the dogs were kept confined and not allowed to exercise. Electrocardiograms showed quite regularly a decrease in the amplitude of the main deflections, with some tendency toward slight predominance of right ventricular effects. The great increase in the length of the diastolic periods coincident with the slowing following the occlusion of the fistulae was regularly recorded electrocardiographically.

4062

Cardiac Hypertrophy in Arteriovenous Aneurysm.*

GEORGE R. HERRMANN AND I. MIMS GAGE.

From the Departments of Medicine and Surgery, Tulane University.

Arteriovenous aneurysm offers an opportunity for the study of factors concerned in the production of cardiac hypertrophy. In the presence of an arteriovenous fistula between the carotid artery and jugular vein, we have confirmed the observation of an immediate enlargement of the cardiac shadow as the fistula is opened. This we feel can be nothing other than dilatation of the heart as a result of the blood shunt. Thus, one of the primary factors in this condition seems to be cardiac dilatation.

It is interesting to note that in a series, 10 dogs in each of which an arteriovenous aneurysm was produced, but thrombosed within a day or two, we found heart weight-body weight ratios ranging from .00690 to .00900, with an average of .00850, which, in our opinion, are not increased enough to be considered significant of actual hypertrophy. The ratios of left ventricular weight were likewise within our normal limits. (See Table I.)

TABLE I.
A-V aneurysm patent for short periods of time.

	Patent	P.O.	L/R	HW/BW
	Hrs.	Mo.		
306	36	4	1.638	.00990
307	48	½	1.230	.00980
310	12	3	1.790	.00690
311	24	½	1.570	.00970
313	36	1	1.260	.00704
314	12	1	1.680	.00970
316	24	2	1.300	.00750
317	12	1	1.820	.00836
319	12	2	1.554	.00810
320	18	1	1.482	.00915
		Averages	1.5	.00850
		Normal	1.4 to 1.8	.00798

In one dog, No. 366, 2 unsuccessful femoral fistulae and one unsuccessful carotid jugular anastomoses were attempted. During these operations the dog had a patent orifice for about a total of 4 days, and at autopsy a H.W./B.W. ratio of .00750 and a L/R ratio of 1.130 were found. In dog No. 355, in which a small slit-like fistula, 3.5 x 1.5 mm., persisted for 80 days, a H.W./B.W. ratio of .01000 and a L/R ratio of 1.420 were found. The left ventricular capacity was 17 cc., while the right ventricle held 14 cc. Dog No. 352, with a 2nd fistula measuring 4 x 2 mm. which had persisted for 40 days (a first, and unsuccessful, fistula had been made 80 days before the 2nd), presented a H.W./B.W. ratio of .01180 which was definitely greatly increased, while the L/R ratio was 1.050. The hypertrophy was thus definitely of the right ventricular type. Dog No. 351, with a carotid jugular fistula 3 x 2 mm. for 143 days, presented the greatest degree of general hypertrophy with a H.W./B.W. of .01250, while the right ventricular predominance was conspicuously indicated by the L/R ratio of 1.000.

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* Aided by a grant from the David Trautman Schwartz Fund.

We may conclude from these preliminary observations that a relatively high grade of cardiac hypertrophy can be produced and that there is relatively greater right ventricular hypertrophy as a result of arteriovenous aneurysm. The left ventricular capacity was 4 cc. and the right ventricle held 5 cc.

4063

Relative Mechanical Strength of Jejuno-Jejunostomies Performed With and Without Intestinal Clamps.

R. A. CUTTING. (Introduced by Henry Laurens.)

From the Department of Surgery, Tulane University Medical School.

The experiments reported in this communication were undertaken in an attempt to elucidate the rôle played by clamps in post-operative recovery from entero-enterostomies, especially with respect to the comparative mechanical strength of wounds made according to a "clamp" or a "clampless" technique. Twenty-nine dogs were used as experimental animals, of which 26 appear in the final report, one having died on the 2nd post-operative day of general peritonitis, and 2 others, though apparently recovering normally when killed and autopsied on the 4th post-operative day, having shown the presence of a small amount of pus in connection with their enterostomy wounds.

Two enterostomies, one with clamps and the other without clamps, were performed in each animal on the same day, the operative procedures consuming a period from November 9, 1927, to March 29, 1928. Enterostomies were performed in the upper jejunum some 10 inches apart and from 12 to 18 inches from the pylorus. The first enterostomy was performed with clamps in the first 13 animals and the second enterostomy in the second 13 animals;

the other enterostomy in each animal was performed with the aid of "guy sutures".

The animals were killed at intervals of one day in such a manner that each post-operative day, up to and including the 12th day, was represented by 2 animals; this was done in a hit or miss manner, however, in such a way as to bring some of the animals appearing early in the operative series late in the autopsy series, and vice versa.

Four segments of intestine, each about 4 inches in length, were cut from the jejunum of each animal at autopsy, the first being cut from the normal gut just proximal to the first entero-enterostomy, the 2nd including the first enterostomy, the 3rd including the 2nd entero-enterostomy, and the 4th being a segment cut just distal to the 2nd enterostomy. The bursting pressure of these segments was measured by forcing air into them and recording, by means of an attached mercury manometer, the pressure at which they burst.

Taking the series as a whole, the 4th segment (segment of intestine distal to the 2nd enterostomy) averaged slightly more than 7% stronger than the first (segment of intestine proximal to the first enterostomy).

The bursting pressures of both of these segments were averaged for each dog, and this figure was taken as the average bursting pressure of the normal intestine in this region. The average bursting pressure thus computed was found to bear no constant relation to the weight of the animal, some of the smaller animals showing relatively high jejunal bursting pressures, and vice versa. On the whole the jejunum of the female animals seemed to show a slightly higher bursting pressure than did that of the males, though this finding was somewhat inconstant. Bursting occurred most characteristically (three-quarters of the cases) at the antimesenteric border of the segments of normal intestine and was both diffuse and explosive, the rent in the peritoneum being usually of considerably less extent than that of the underlying tunics. Less frequently the rupture occurred at the mesenteric border, and still less frequently at a point intermediate between the 2.

The percentage strength of the 2 enterostomies was computed by dividing their bursting pressures by the bursting pressure of normal intestine as computed above; this was done, of course, separately for each animal. Enterostomies by both methods and on all post-operative days show marked variations in strength, but they were about one-third as strong as normal gut immediately after their performance, progressively decreased in strength for 3 days, then rapidly and progressively rose to, or exceeded the strength of normal gut on the 10th day, then suddenly decreased on the 11th day to about half-strength, again being on the increase on the 12th day. Entero-enterostomies performed with clamps are somewhat stronger than those performed with guy sutures, especially on the 2nd, 3rd, and 4th days, this being the critical period in repair.

4064

Effect on the Immunity Mechanism of Various Avitaminoses.

S. N. BLACKBERG. (Introduced by Dr. J. T. Halsey.)

From the Department of Pharmacology, Tulane University.

Various authors[1, 2, 3] have shown that avitaminosis increases the susceptibility to both bacterial invasion and to bacterial toxins.

In this laboratory, in several groups of white rats deprived of vitamins A and D, or B, or E, it has been found that the resistance to tetanus toxin, of these avitaminic animals, is very markedly diminished when compared with that of the normally nourished controls (from 40 to 100 times less).

In other series the effect of these avitaminoses on the formation of agglutinins and bacteriolysins was investigated by the usual methods of injecting typhoid bacilli, under constant conditions into avitaminic and control groups.

The results may be briefly summarized as follows:

After several injections of killed typhoid cultures, the serum of the avitaminic animals regularly showed a much lower agglutinin titre and less bacteriolytic power than that of the normally nourished controls. Following the injections of living typhoid bacilli, a similar but slighter difference was found in the serum of the avitaminic and control groups. With the injection of larger amounts of living bacilli it was manifest that this difference became progressively less. This latter finding appears to be well explained by the view that in the living cultures there were present sufficient amounts of the different vitamins to overcome, at least in part, the deficiencies of the diet. The increase in weight and the improvement of general conditions of the avitaminic rats, after receiving these larger amounts of the living cultures, seems to furnish evidence for the

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[1] Werkman, C. H., *J. Infect. Dis.*, 1923, xxxii, 247.

[2] Findlay, G. M., *J. Path. and Bact.*, 1923, xxvi, 1.

[3] Findlay, G. M., *ibid.*, 485.

correctness of this view. Investigations of the effects of lack of these vitamins on the antitoxin production are under way.

4065

Sensitivity of Isolated Intestine of Athyroid, Normal and Thyroxinized Rabbits to Physostigmine and Adrenalin.

CHAPMAN REYNOLDS.

From the Department of Pharmacology, Tulane University.

It is generally accepted that increased thyroid secretion "sensitizes" the autonomic nerves, particularly the sympathetic. Evidence that this is so has been presented by Eppinger, Asher, Oswald, Cannon, Levy,[1] and others. The usual experimental method has been the quantitative determination of the blood pressure change induced by adrenalin, but "acute" experiments with thyroid substance or thyroxin have been generally negative.[2] The isolated intestine is such a delicate physiological test-agent, responding to both sympathetic and parasympathetic stimuli, that it was thought that investigation of the behavior of such segments in the presence of greater or less amounts of thyroid product might disclose significant differences. "Acute" experiments (*i. e.,* dropping thyroxin in one bath and not in the other of parallel segments) were done some years ago and were uniformly negative.

The plan of the present work was as follows: rabbits were thyroidectomized under local anesthesia without disturbing the parathyroids and about 2 or 3 weeks later their isolated intestinal responses were studied in the usual fashion in a Tyrode bath. During the same period other rabbits were given 2, 3 or more 0.1 mg. doses of thyroxin intravenously, and the sensitivity to autonomic stimulating drugs compared quantitatively with segments from the thyroidectomized and normal animals. Comparisons were always made simultaneously in order to be sure of uniform temperature, oxygen and other environment.* To insure a fair distribution of the drugs administered, a double-chamber bath as shown in Fig. 1

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[1] Levy, R. L., *Am. J. Physiol.,* 1916, xli, 492.

[2] Feldberg and Schilf, *Arch. f. exp. Pharm. u. Path.,* 1927, cxxiv, 94. Herzfeld and Mosler, *Klin. Woch.* (Berlin), 1926, v, 1281.

* Keeping the intestine in a thyroxin solution from the time the animal was killed until observation was begun was tried a few times and made no apparent change in responses.

was used. The recording segments were suspended in chamber A. The drug was run into chamber B through the oxygen tube C and allowed to diffuse throughout this chamber before it was mixed with the fluid in A by gentle blowing through tube D. The whole system was immersed all the while in a constant temperature bath.

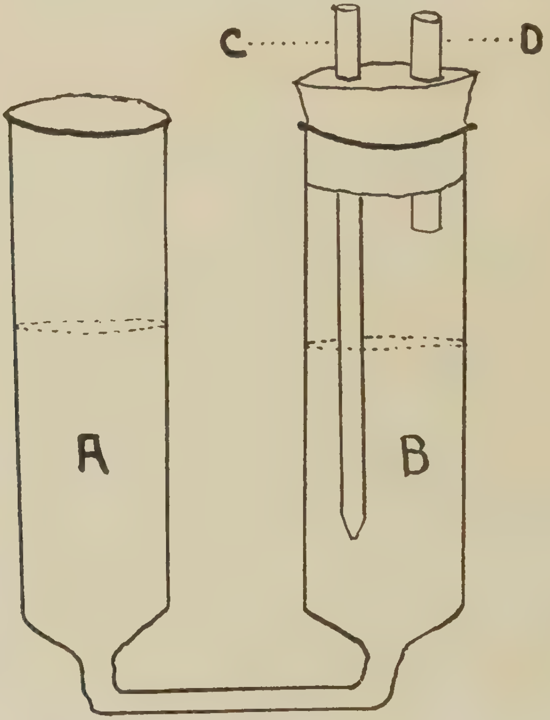

FIG. 1.

Adrenalin. Duodenal segments from normal, athyroid and thyroxinized animals showed no significant or constant difference in their response to this drug (20 experiments), perhaps because, owing to the instability of this substance in the somewhat alkaline Tyrode's solution, it was impossible to obtain simultaneous contact of the same concentration of adrenalin with the two segments.

Physostigmine. In 16 experiments, 12 showed a greater sensitivity in thyroxinized than in athyroid segments, 2 showed less, and 2 were apparently equal in response. In 5 of 6 experiments in which segments from thyroxinized animals were compared with those from normals, the response of the thyroxinized gut was greater than that from the control, while in one it was apparently equal. (Greater sensitivity was manifested by either a response to lower drug concentration or by earlier or markedly greater degree of response to the same concentration. A typical result is shown in Fig. 2.)

The indication of sensitization to parasympathetic stimulation may or may not have been accidental in view of the fewer contradicting negatives.

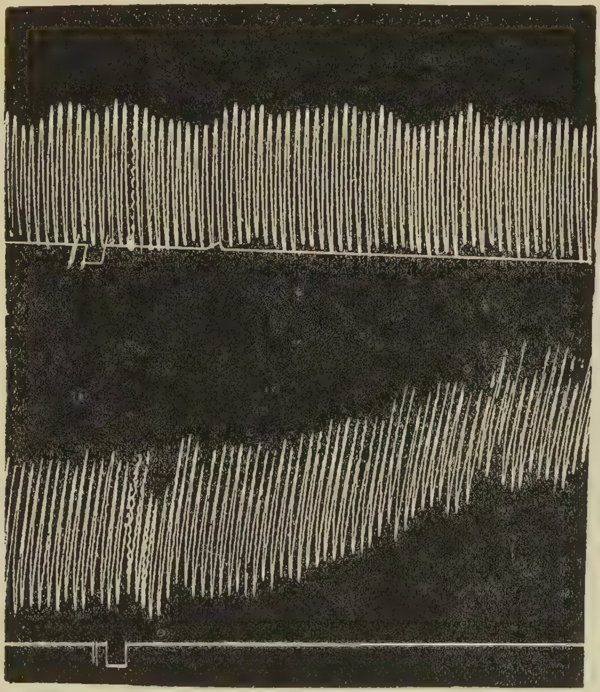

FIG. 2.

Upper curve is tracing from duodenal segment from athyroid, lower from thyroxinized rabbit, suspended in same bath. At signal physostigmine (1:12 million) was brought in contact with both segments.

4066

A New Dialysis Test for Tissue Thirst.

WILLIAM A. THOMAS AND EDMUND ANDREWS.

From the Department of Surgery, University of Illinois College of Medicine and the Surgical Service of St. Luke's Hospital, Chicago.

Small samples of blood serum from normal and nephritic individuals have been dialyzed against water, normal salt solution, and various strengths of weak hydrochloric acid. This was done on the assumption that in edematous individuals the colloids were already saturated with water and would swell less on dialysis than in the normal. To our surprise the reverse proved true. In a long series of experiments this phenomenon has been constant and so striking that we believe the method may be of real clinical value.

The technique is as follows: Tubes about 15 cm. long were prepared with a small bell-shaped opening. The opening was closed with a thin collodion membrane and one or 2 cc. of serum introduced into the tube with a fine bacteriological pipette. The tubes are calibrated so that when filled to a certain point and immersed in fluid the amount of swelling can be read in percentage of the original volume of the serum. The results of these studies are as follows:

1. The maximum swelling takes place with N/100 HCl.
2. Normal sera generally do not swell at all, but never more than 9%.
3. Sera from a long series of cases of uremia and oedema, both nephritic and cardiac, swell enormously. (Very often over 50%, the maximum tube reading.)

Careful studies of the chemical composition of these sera showed that the swelling was dependent neither on the acidosis (as measured by carbon dioxide combining power, Van Slyke), the urea content, the sodium chloride content, or the protein content of the sera. In fact the edematous and nephritic sera invariably contain less protein than the normal sera although they swell very much more.

Experiments were performed by adding salt, urea, etc., to the sera and that did not increase the swelling. From these studies it is evident that in nephritis and edema there is some change either in the chemical composition or the colloid dispersion of the proteins themselves which render them capable of absorbing far larger amounts of water than normal sera.

New York

4067

Effect of Intravenous Bacterial Filtrates on Skin Tests and Local Infections.

FRANKLIN M. HANGER, JR. (Introduced by A. R. Dochez.)

From the Department of Medicine of the College of Physicians and Surgeons, and the Presbyterian Hospital, New York.

In a previous report[1] we have shown that rabbits are often naturally allergic to filtrates of many gram negative bacteria. It was suggested that this allergy is due to the overwhelming predominance of gram negative organisms in the upper respiratory tract of these animals and to the fact that chronic infections are quite common in this region. Positive skin tests are given not only to broth filtrates of *B. lepisepticum* and other bacteria representing the normal nasopharyngeal flora, but to the other organisms such as *B. coli, B. influenzae* and even to such an organism as meningococcus, to which the animal has never been directly exposed. Rabbits lacking this natural allergy develop it about one week after infecting the skin with a virulent strain of *B. lepisepticum.* In fatal infections, skin allergy does not appear. When large necrotic lesions develop, a positive skin test may not be elicited until the 15th day or later, but before healing begins, it becomes quite striking and is of valuable prognostic import. The intensity of reaction usually recedes with the clearing up of the infection and the development of a generalized immunity. During this phase of acquired allergy, the animal reacts non-specifically to the filtrates of many gram negative organisms of widely different groups.

When filtrates of strains of *B. lepisepticum* and other gram negatives are injected intravenously, the reaction is quite different in the allergic and non-allergic rabbit. The highly sensitized animal often develops diarrhea about 20 minutes after the injection. He rapidly goes into shock and dies in convulsions within a few hours, even when one cc. or less of the filtrate is used; while the non-allergic animal usually will survive 15 cc. or more without marked symptoms. Filtrates from highly virulent strains of *B. lepisepticum* occasionally will kill a non-allergic rabbit. Rabbits completely recovered from a severe *B. lepisepticum* infection and with skin reactions still moderately strong, show no ill effects from very large doses of the filtrate. The striking lesion in animals dying from filtrate injections is marked congestion of the lungs and bronchi with hemorrhage. Occasionally there are hemorrhages in the skin and other organs.

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[1] Hanger, Franklin M., PROC. SOC. EXP. BIOL. AND MED., 1927, xxv, 230.

Skin tests made within an hour of intravenous injections of potent filtrates are negative even in animals that usually give strong reactions. Various bacterial suspensions and India ink intravenously produce a similar effect. Skin reactivity is often permanently diminished in an animal receiving one or more intravenous injections. When the skin test precedes the intravenous filtrate by several hours, obliteration does not occur, but an *intensification* of the local reaction is seen, and the site of inoculation often shows bluish discoloration with areas of petechial hemorrhages. In most instances, an extensive local necrosis occurs. Histologically the lesions show marked swelling and disruption of the capillary endothelium. There are minute thrombi in these vessels and many red cells loose in the intercellular spaces. We have never observed this phenomenon except among rabbits naturally allergic (See chart of animals 192 and 198) or rendered allergic by a previous infection. (See chart of animals 208 and 153.) The intensity of the reaction is roughly proportional to the allergy of the animal to the filtrate used. Necrosis is most extensive when the skin test is made 24 hours before intravenous injection and is rare when less than 12 or more than 48 hours have elapsed.

This reaction appears to be non-specific. Skin test sites made with filtrates of R. D. (a virulent strain of *B. lepisepticum*) or of 24/3 and X (non virulent strains of *B. lepisepticum*) or of a colon bacillus, react similarly when a variety of filtrates are given intravenously (See Animals 153 and 150). Occasional rabbits show slight natural allergy to filtrates of streptococcus (See Rabbits 172 and 192). In such animals skin reactions induced by filtrates of *Streptococcus* likewise become hemorrhagic or necrotic when filtrate of one of the above mentioned gram negative organisms is given intravenously. Non-specific irritants such as turpentine, rarely give the reaction (See Rabbits 192, 169, 137 and 172), while plain broth controls have been constantly negative.

We have made but few attempts to study the influence of immune serum on this phenomenon. Rabbits infected with *B. lepisepticum* form agglutinins and precipitate rather poorly. The serum of such immunized rabbits fails to prevent necrosis as is shown in 198.

We have never succeeded in producing necrosis by injecting filtrate directly into the 24 hour skin test site. It is rather obscure why the filtrate diluted in the blood is more destructive to endothelium than the same filtrate concentrated locally.

Animals suffering from acute or chronic R. D. infections die very readily after receiving a potent filtrate intravenously. Blood cultures which have been proven sterile before the injection subsequently often become positive. An infected skin lesion seldom becomes larger as a result of the filtrate inoculation, but often assumes the purplish hemorrhagic hue shown by the skin tests. Closely related to this phenomenon is the observation that many rabbits after receiving filtrate intravenously develop a clear watery nasal discharge which often becomes purulent within a few days. Typical snuffles follows. It seems probable that these animals are suffering from a latent upper respiratory infection with *B. lepisepticum* and that such small foci react with increased intensity to the injection of antigen. This phenomenon is analogous to focal reactions induced by tuberculin injections in tuberculous individuals.

4068

Genetic Relations of Chocolate Brown Plumage Color in the Domestic Pigeon.

DEWEY G. STEELE. (Introduced by L. L. Woodruff.)

From the Osborn Zoological Laboratory, Yale University.

All of the numerous color modifications known in the domestic pigeon may be grouped under 3 basic types of pigmentation; black, chocolate, or red. Of these 3 types black and red are by far the best known. Their genetic relationships were fully studied by Cole.[1] Chocolate has long occurred in several varieties of pigeons but the breeder has commonly classed this color with dun (dilute black). It was first recognized as a distinct type of pigmentation by Metzelaar.[2] Three years later Christie and Wriedt[3] reported chocolate

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[1] Cole, L. J., *Rh. Is. Agric. Exp. Sta. Bull.*, 1914, 158, 311.

[2] Metzelaar, J., *Am. Pigeon Keeper*, 1924, xxvi, 22.

[3] Christie, W., and Wriedt, C., *Z. f. ind. Abst. u. Vererb.*, 1927, xliii, 391.

TABLE I.*

Results of reciprocal P_1 crosses of chocolate x black and chocolate x red matings.

No. of matings	Type of mating	Results				Total
		Black		Choc.		
		♂	♀	♂	♀	
2	Black ♂ — E(E) B(B) Choc. ♀ — E(E) b—	8	4	0	0	12
3	Choc. ♂ — E(E) bb Black ♀ — E(E) B—	10	0	0	12	22
1	Red ♂ — ee B(B) Choc ♀ — E(E) b—	7	10	0	0	17
2	Choc. ♂ — E(E) bb Red ♀ — ee B—	1	0	0	5	6
		Total				57

* Combining data obtained at the University of Wisconsin and Yale University. About 15 F_1 birds have been omitted because the sex records have not been obtained for them. The results of the linkage studies between the B and I factors will also be presented later.

recessive and sex-linked in relation to black. The data here presented confirm their conclusion. The results of the chocolate x recessive red matings are also in general agreement with those just published by Metzelaar.[4] When the male parent is red and the female chocolate, blacks occur in both sexes in the F_1. These results demonstrate an interaction between a factor for black carried by the red parent with an extension factor from the chocolate. In the reciprocal matings the results are modified by the sex-linked relations of the B factor. The data are presented in Table I, and an inspection of the results will show that the genetic relationships of the 3 basic color types in pigeons may be interpreted upon the basis of a 2 factor hypothesis. The factors are:

B—factor for black, b—chocolate, sex-linked.

E—factor for extension of black or chocolate, e—non-extension.

The linkage relations between chocolate and the intensity factor are being studied, and present results (2 crossovers: 7 non-crossovers) indicate a rather loose linkage between these factors. The pigment obtained by chemical extraction from chocolate feathers greatly resembles black in its general appearance but in solubility tests it seems more like red.

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[4] Metzelaar, J., *Occasional papers of the Museum of Zoology*, Univ. of Mich., 1928, 194, 1.

4069

Pleural Reactions to Primary and Secondary Infection with Tubercle Bacilli.

M. M. STEINBACH. (Introduced by F. P. Gay.)

From the Department of Bacteriology, College of Physicians and Surgeons, Columbia University.

It has been shown[1] that the pleura of a guinea pig, previously sensitized to tubercle bacilli, reacts differently from the pleura of a non-sensitized pig. Paterson obtained a reaction on injecting varying amounts of from 0.001 gm. to 0.00001 gm. of tubercle bacilli in sensitized animals, and no reaction in non-sensitized animals unless the dose was 0.002 gm. or more.

If tuberculous pleural effusion develops in the human chest after days or weeks of febrile reactions, the patient usually gets well or improves, the fluid is absorbed, and thickening of the pleura takes place, unless the lung is too actively involved. The object of our study has been to determine whether tuberculous pleurisy with effusion is essentially a protective mechanism and how it is produced.

Thirty adult guinea pigs averaging 650 gm. were tested with O. T. intracutaneously and were found to be negative. Fifteen of these pigs received 0.1 mgm. RI (Trudeau) of a relatively avirulent strain of human tubercle bacilli subcutaneously into the right groin. Three weeks later they gave a positive tuberculin reaction. Fifteen of the animals were left untreated; 68 days later the 15 sensitized and the 15 untreated pigs received intrapleurally 0.001 mgm. of a more virulent strain of bacilli H-305 in 1 cc. saline. The 30 pigs were then tested as follows:

(1) Five of the sensitized and 5 of the non-sensitized pigs were tapped and aspirated at 24-hour intervals for a period of 5 consecutive days, and cellular studies made of the fluids.

(2) The second set of 5 sensitized and 5 non-sensitized pigs were killed at the same time intervals as above, and studies were made of the fluids, thickening, adhesions, and the dissemination.

(3) The third set of 5 sensitized and 5 non-sensitized pigs were permitted to live in order to study the length of life and difference in distribution between the aspirated and non-aspirated animals.

Following reinfection fluid was obtainable in small amounts varying from 0.3 to 2 cc. in nearly all the sensitized animals during the first few days. None of the controls showed an immediate exudate but some of them developed fluid weeks or months after inoculation. This latter finding may be explained by endogenous reinfection. Cellular studies were made on the fluids obtained. In the sensitized animals there was an immediate response of fluid containing large amounts of polymorphonuclear leucocytes varying from 80% to 92% in the first 24 hours, with a gradual replacement of the polymorphonuclear leucocytes by clasmatocytes. On the 4th and 5th days the clasmatocyte count varied from 72% to 100%.

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[1] Paterson, Robert C., *Am. Rev. of Tuberculosis*, 1917, i, 353.

In order to determine the type of cells that may be found in the non-sensitized animals (controls), where no immediate exudate is present, 0.1 cc. of broth was used to wash out the pleural cavity. From the first to the 5th day after reinfection the predominating cells in the washed cavities were clasmatocytes varying from 96% to 100% as is true in normal animals (Gay and Morrison).[2] The white count varied from 1,750 to 12,750 cells per cu. mm. Whether there is an increase in total clasmatocytes and white cells in these infected controls over the normal animals is still under investigation. Adhesions and thickening of the visceral, parietal, and diaphragmatic pleura averaged 70% in the sensitized animals within the first 5 days, whereas no adhesions, thickening, or fluid were found in any of the non-sensitized animals even with an intrapleural dose of 5 mgm. of H-305.

Intrapleural injections of small doses of tuberculin gave no pleural reaction in either sensitized or non-sensitized animals. Emulsions of dead streptococci gave no reaction in sensitized or non-sensitized animals, but the injection of 0.1 mgm. RI or 0.001 mgm. H-305 gave a positive reaction in 17 out of 20 sensitized animals. Thickening and adhesions were encountered in all the sensitized animals that were permitted to live on. The degree of thickening varied from fine adhesions to complete obliteration of the pleural cavity, with marked adherence of lung to the chest wall. Thickening and adhesions were also found in 20% of the non-sensitized animals weeks or months after infection.

In 40% of sensitized animals tubercle bacilli were found in the exudate 1 to 5 days after reinfection. In the non-sensitized animals no tubercle bacilli were found when 0.001 mgm. H-305 was used as the dosage. When 5 mgm. were used 40% of the broth washings from the non-sensitized animals were found positive for tubercle bacilli.

The difference in the length of life of the sensitized and non-sensitized animals has not as yet been determined.

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[2] Gay, F. P., and Morrison, L. F., *J. Am. Med. Assn.*, 1923, lxxx, 1298.

Conclusions: To obtain an immediate pleural reaction by means of tubercle bacilli, previous sensitization appears necessary.

Tuberculous pleurisy in guinea pigs would appear to be a reinfection as is believed to be the case in man.

The reaction of the sensitized pleura on reinfection with tubercle bacilli is another illustration of the Koch phenomenon, and offers advantages for the study of the protective significance of this reaction.

4070

Philippine Fowl Disease.

E. A. RODIER. (Introduced by Earl B. McKinley.)*

From the Veterinary Research Laboratory, Bureau of Agriculture, Manila, P. I.

What is believed to be a new disease of fowls recently appeared in the Philippines. The epizootic began in September, 1927, and proved to be highly contagious. The first case of the disease appeared in Manila and rapidly spread over an area having a radius of about 50 miles with Manila as the center of the infection. By February 1, 1928, it has been estimated that at least 50,000 fowls have succumbed as a result of this disease. Both males and females are affected and fowls of all ages are susceptible. The disease has been prevalent in chickens, and a few cases have been noted in ducks and geese.

Symptoms: The onset of the disease is sudden. Chickens at first show an indisposition to move about, preferring to sit or stand quietly in a secluded spot. Very early in the course of the disease there is a diarrhea which gradually improves if the fowl is to recover. Gasping for air associated with jerking movements of the head downward and backward is a characteristic symptom. This is caused by large quantities of tenacious mucus which obstructs the posterior nares and pharynx. Many fowls die of suffocation early in the course of the disease. Excessive thirst is noted in many cases and the crop is often filled with large quantities of water and mucus as well as foul smelling gas in some instances.

Occasionally there is a bloody diarrhea but this is not a common symptom. The fowls usually die within 1 to 7 days following the onset of symptoms. If the fowl is to recover from the disease the mucus in the nose and throat disappears but the fowl gradually develops a paralysis of the legs which may be either unilateral or bilateral. Of those fowls which recover from the acute symptoms and develop paralysis only a small percentage (about 5%) fully recover from the paralysis. Paralyzed fowls may live for indefinite periods provided they are fed by hand and given water at regular intervals by medicine dropper. Fully 99% of fowls develop paralysis if they survive the acute stages of the disease.

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* This preliminary report has been prepared by Dr. McKinley and will appear in this form in his forthcoming review of the filterable virus diseases.

The Philippine fowl disease is similar in some respects to other diseases known to occur in fowls. It is similar to infectious bronchitis of fowls in that there is the characteristic posture of the sick fowl, head extended, beak open, gasping for breath in both conditions. The paralysis somewhat resembles the chicken paralysis disease of fowls which has been described by Pappenheimer, Dunn, and Cone, but is different from this disease in many of its other clinical manifestations. In the early stages the Philippine fowl disease resembles both infectious and nutritional roop. It is similar to fowl pest especially in the per-acute cases which die within 24 hours. Fowl pest is transmitted by minute quantities of blood to healthy fowls, but this disease is not so transmitted.

Pathology: Up to the present only the gross changes have been studied. The disease is essentially an infection of the alimentary tract. There is a peri-esophageal inflammation in all cases which may involve the crop and extend throughout the entire length of the esophagus. This inflammation is accompanied by hemorrhages which vary in size from small petecheal hemorrhages to large hemorrhagic streaks or extravasations of blood. The changes in the intestinal tract are hemorrhagic in nature and vary greatly in degree. Petecheal hemorrhages are also found on all the serous membranes. The eyes, nose and throat are all filled with a tenacious glary mucus during the first days of the disease and the crop frequently contains large quantities of this material. Histologic studies have only been made of the brain and cord taken from fowls during the stages of paralysis, but no definite changes have been found so far in the small amount of material which has been examined.

Etiology of the Disease: No bacterial incitant of the disease has been recovered from infected animals. The disease can be transmitted to healthy fowls by feeding the washed tissue of the intestinal wall. The disease can also be transmitted by subcutaneous inoculation of an emulsion of the intestinal mucous membrane which has been passed through a Berkefeld N filter. Rodier infected 10 out of 11 fowls which he inoculated with a Berkefeld filtrate of the intestinal mucous membrane. All developed typical symptoms of the disease with the exception of one. In another experiment 13 fowls were inoculated with a Berkefeld filtrate of an emulsion prepared with the contents of the crop. Of these, 10 fowls developed typical symptoms of the disease while 3 appeared to be resistant. The virus is apparently present in the blood stream of infected fowls only in the early stages of the disease. Bacteria isolated from the feces of infected animals appear to be innocuous. Injection of liver, kidney and lung tissues from infected fowls into healthy fowls produces the disease in some instances. Bile in 1 instance has proved infective. Brain emulsions prepared from brain tissue of birds which have died of the disease have in all instances proved negative.

No attempts to cultivate the virus of this disease have as yet been made. From these preliminary experiments there appears to be strong evidence that this disease is caused by a filterable virus and that the disease represents a disease of fowls heretofore unknown. Since January the spread of the disease has been effectively checked by rigid quarantine measures. The causative filterable virus has been passed serially through a large number of fowls and a more complete study of the virus, the disease, and its pathology is contemplated.

4071

Recovery of Excitability in the Turtle Ventricle.

HAROLD F. BLUM, JEANETTE ABBOTT AND KATHLEEN KILGARIFF.

From the Department of Animal Biology, University of Oregon, and the Rudolph Spreckles Physiological Laboratory, University of California.

Ashman and Hafkesbring[1] report a progressive increase in the excitability of turtle ventricle with repeated stimulation, *i. e.*, a treppe of excitability. One of us in a recent study[2] on the recovery of contractility in turtle ventricle, has indicated that the treppe in contractility depends upon the alteration of the rate of recovery after contraction. And further, that this rate of recovery varies with 2 factors: (1) the amplitude of the preceding contraction, and (2) the interval between the 2 preceding contractions. In the course of the experiments leading to these conclusions certain observations were made on excitability which were not published at that time.

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[1] PROC. SOC. EXP. BIOL. AND MED., 1928, xxv, 525.

[2] Blum, H. F., *Am. J. Physiol.*, 1927, xxxii, 157.

In these experiments ventricular strips were caused to contract rhythmically by the application of electrical stimuli. It was found that when an extra contraction was produced following one of the regular rhythmical responses (by the introduction of an extra stimulus), the absolute refractory period following this contraction is shorter than that following the regular rhythmical contractions. As an example: Ventricular strip responding rhythmically every 4.4 seconds. Very strong stimuli ineffective during interval of 2.1 seconds following the rhythmic responses. Response obtained at 2.2 seconds after one of the regular contractions. Following this response another was elicited with the same strength of stimulus after only 2.0 seconds.

The foregoing experiment indicates that the recovery of excitability is more rapid after 2 contractions which follow closely upon each other than when these contractions are separated by a longer interval of time. Thus it appears that the rate of recovery of excitability depends upon the interval between preceding contractions. These findings parallel those for the mechanical responses,[2] and are quite in accord with those of Ashman and Hafkesbring.

Further experiments are in progress which it is hoped may assist in the explanation of the treppe in excitability and the summation of stimuli.

4072

Iodine Poisoning Counteracted by Thiosulphate.

HAROLD B. MYERS AND CHARLES FERGUSON.

From the Department of Pharmacology, University of Oregon Medical School.

Sabbatini[1] called attention to the action of thiosulphate of sodium in removing the stain of iodine from the skin. Thiosulphate is a component of the relatively non-toxic, so called colorless tincture of iodine. Its ability to bind with iodine apparently takes precedence over the combination iodine forms with the protein of the tissues. Sollmann[2] has reported upon "The Fate of Iodin, Iodids and Iodates in the Body," showing that free iodine is promptly bound and circulates as iodide, bound through protein. The possibility is presented of thiosulphate combining with iodine absorbed and circulated in protein combination in a manner similar to that observed in superficial tissue.

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[1] Sabbatini, L., *Gaz. Osp. e Clin.*, 1912, xxxiii, 58.

[2] Sollmann, T., *J. Pharm. and Exp. Ther.*, 1917, ix, 269.

Boehm[3] has shown that dogs injected intravenously with a lethal quantity of compound solution of iodine (40 mgm. per kilo) exhibit no symptoms of toxicity for a period of 4 to 6 hours. Death is usually delayed for many hours. Pathology due to the iodine, found at autopsy, is produced in similar manner by iodide of sodium. In fatal iodine poisoning in man, death is usually delayed over a period of 24 to 48 hours, offering a favorable time interval for effective intervention.

Rabbits were injected subcutaneously with tincture of iodine, diluted to one-third strength with water, at the time of injection. The minimal lethal dose was found to be 0.175 to 0.180 gm. per kilo. No rabbit receiving more than the latter amount survived. Thiosulphate of sodium in 10% strength produced no toxic symptoms in dosage of 3.0 gm. per kilo, subcutaneously injected.

The iodine solution was injected beneath the skin of one lateral half of the body, thiosulphate solution subcutaneously on the opposite side.

Rabbits injected with twice the lethal dose of iodine exhibited but slight evidences of toxicity when thiosulphate was used. It was found advisable to give small amounts of thiosulphate by stomach tube at intervals of 3 or 4 hours during the first 12 to 15 hours of the poisoning, to avoid inflammation of the gastric mucosa. Food was then accepted readily. Thiosulphate injected intravenously caused rapid disappearance of symptoms of toxicity. Best results were obtained by combining subcutaneous, oral and intravenous methods of administration. The dosage of iodine was increased to 0.450 gm. with recovery. Iodide of potassium, as a constituent of the tincture was present in the amount of 0.321 gm. additional to the iodine. No attempt was made to increase the dose of iodine above this amount.

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[3] Boehm, R., *Arch. f. Exp. Path. u. Pharm.*, 1876, v, 329.

4073

Effect of Morphine in Moderate Doses Upon Growth of the White Rat.

HAROLD B. MYERS AND JOHN B. FLYNN.

From the Department of Pharmacology, University of Oregon Medical School.

Sollmann[1] reported upon the growth of rats chronically poisoned with morphine, showing that a material increase in weight over that of control animals occurred for a time, followed by a sharp decline in the weight curve after 11 weeks of morphine feeding with as little as 2.5 mgm. of the drug per kilo weight. The rats fed morphine showed a preference for the poisoned food, eating more readily of it than of similar food not containing morphine. The primary increase in weight might be explained, in part at least, on the basis of greater food consumption.

Hildebrandt[2] reports little change in the weight of rats injected subcutaneously with morphine, during the first 2 weeks, succeeded after a period averaging 4 weeks with pronounced loss of weight. He began injections with 100 mgm. morphine, increasing the dose rapidly to amounts of 600 to 1000 mgm. per kilo. An increased metabolism was found in the morphine poisoned rats by Hildebrandt.

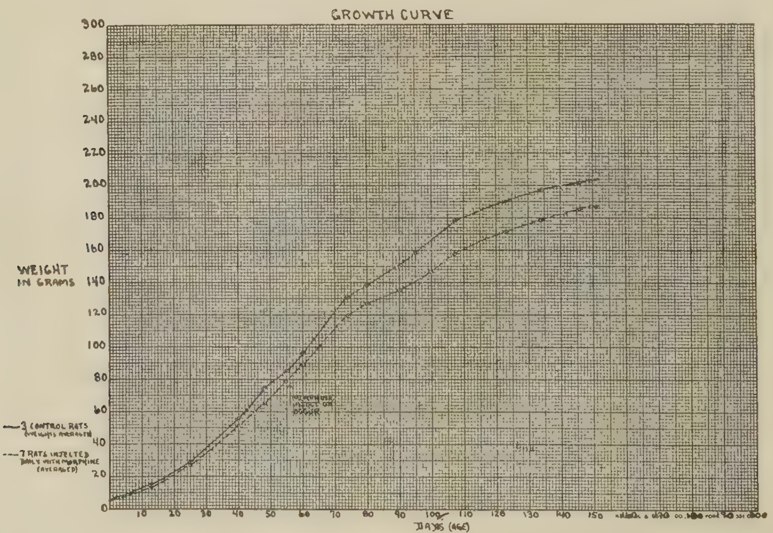

FIG. 1.

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[1] Sollmann, T., *J. Pharm. Exp. Ther.*, 1924, xxiii, 449.

[2] Hildebrandt, F., *Arch. Exp. Path. Pharm.*, 1922, xcii, 68.

Two series of rats were injected daily with morphine, the first group consisting of young animals, the second of mature rats. Morphine injections were begun in the first group on the 56th day of life. Ten injected animals were divided into 5 pairs according to dosage, ranging from 1 to 5 mgm. per kilo. A moderate impairment in growth weight was observed, as shown in the average curve in Fig. 1.

The mature animals chronically poisoned with morphine in uniform dosage gradually increased to 10 mgm. per kilo showed a decreased increment in the weight curve quite analogous to that observed with the young rats. The average curves for the second series are shown in Fig. 2.

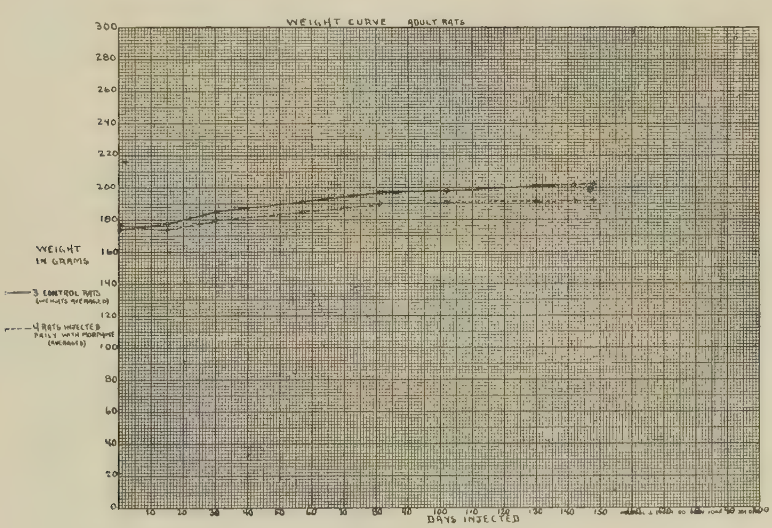

FIG. 2.

No difference in observable activity, desire for food, alimentary disturbances or other departures from the condition of the control animals was observed to account for the impaired weight curves in the morphine poisoned rats.

One may conclude that young rats injected daily with morphine in dosage of 1 to 5 mgm. and mature rats given up to 10 mgm. per kilo weight exhibit a moderate handicap in growth and mature weight, respectively.

4074

Hemopoietic Effect of Nuclear Extractives From Kidney, Pancreas and Spleen in Experimental Hemolytic and of Human Pernicious Anemia.*

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From the Departments of Anatomy and Medicine, University of Oregon Medical School.

Previously reported[1, 2, 3] experiments on the effect of nuclear extracts in anemias have led us to an extension of the source of material elsewhere than to fowl's blood and beef liver. The present report will deal with the hemopoietic effect of extracts obtained by the methods of Hammarsten and of Kossel-Neumann from kidney, pancreas and spleen on experimental rabbits, and with the effect of similarly obtained extracts from liver and spleen on pernicious anemia in human patients.

Experimental anemia was produced in rabbits by repeated injections of water intravenously. Six control animals were run without further treatment, after a degree of anemia corresponding to that of the treated animals had been produced. One of the controls died, apparently as a result of the water injection. Averages for the 5 remaining show an increase from 3,638,000 to 6,040,000 erythrocytes per cm. in 26 days. This result corresponds closely with that from a previous series[3] of controls similarly treated. The reticulocytes did not increase beyond 3%.

A second series of rabbits was treated with extract from beef kidney. Two of these animals were treated without having been made anemic. They showed an increase from 5,850,000 to 6,580,000 and from 5,670,000 to 6,876,000 erythrocytes per c. mm., respectively, in 6 days. On the 6th day the reticulocytes numbered 12% in each case. The erythrocyte count continued to increase to a high point of 7,620,000 and 7,680,000 per c. mm., respectively, in 21 days. The hemoglobin showed corresponding increases. Two anemic rabbits treated with extract from kidney showed an increase

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* Aided by a grant from the Research Committee of the American Medical Association.

[1] Larsell, O., Nokes, H. T., and Phillips, B. I., *Arch. Path. and Lab. Med.*, 1926, ii, 698.

[2] Larsell, O., Jones, N. W., Nokes, H. T., and Phillips, B. I., *J. Am. Med. Assn.*, 1927, lxxxix, 682.

[3] Larsell, O., Jones, N. W., Phillips, B. I., and Nokes, H. T., *J. Am. Med. Assn.*, 1928, xc, 75.

in erythrocyte count from 3,640,000 to 6,980,000 and from 3,600,000 to 6,580,000 per c. mm., respectively, in 12 days. The hemoglobin increased from 58% to 112% in one case and from 52% to 115% in the second rabbit during the same period. The high point in reticulocyte percentage was 12% and 10%, respectively, in each case on the 5th day.

A third series of 6 anemic rabbits was treated with extract from beef pancreas. One choked to death as a result of forcible feeding of capsules containing the extract. The remaining 5 animals showed a return from an average low count of 3,620,000 erythrocytes per c. mm. to 6,012,000 per c. mm. in 15 3/5 days. The highest reticulocyte percentage noted was 6% on the 10th day after beginning treatment. A 4th series of 6 rabbits, treated with extract from beef spleen, showed increase from a low average of 2,978,000 erythrocytes per c. mm. to an average of 5,850,000 in 10½ days. The average high point in reticulocyte percentage was 48% on the 5th day. Some of the animals showed the high point in reticulocytes earlier than the 5th day and some as late as the 9th day. In all cases the pancreas and spleen extract treatment brought about a marked increase in hemoglobin percentage also. In rabbits treated with pancreas extract the hemoglobin increase was from a low average of 57% to 102% in 10 days. The animals treated with spleen extract showed an increase from a low average of 50% to 98% in 8 days.

Pernicious Anemia. Twenty human patients on whom a diagnosis of pernicious anemia had been made after the usual tests have been treated to date with the extract produced by the method used by us from liver, and 3 cases have been treated with the spleen extract. The majority of these patients have responded favorably to the treatment, but in varying degree. One case from each group may be described briefly. Patient W. L. was placed under treatment with our extract from liver, showing at the beginning of treatment an erythrocyte count of 1,728,000 per c. mm., hemoglobin 41% (Haskins-Sahli), color index 1.13, volume index 1.23, and with clinical symptoms of pernicious anemia. He was given 6 gm. daily of the extract. Four days after treatment began the reticulocyte percentage had increased to 8%, on the 5th day to 10%, on the 9th day to 21%, and on the 11th day to 24%. Following this there was a gradual decline in reticulocytes, until after 41 days there were only 2% of these corpuscles. In the meantime the erythrocyte count had increased to 5,120,000 per c. mm. in the 41 days, the hemoglobin to 104% (Haskins-Sahli), and the color index was reduced to 1.06. Marked clinical improvement began about the 11th day of treatment.

A second patient, J. McC., had a history of periodic attacks of anemia for 3 years. When the present treatment was begun he had an erythrocyte count of 2,160,000 per c. mm., hemoglobin 56% (Haskins-Sahli), color index 1.15, and reticulocytes 1.4%. He was given 9 gm. daily of nuclear extract from spleen. In 3 days the reticulocytes increased to 20%, in 6 days to 34%. Fourteen days after treatment was begun the reticulocytes had dropped again to 12%, and after 24 days to 4%, at which level they remained 31 days after treatment was begun. In the meantime the hemoglobin had increased from 55% to 100%, and the erythrocytes from 2,048,000 to 4,500,000 per c. mm., in the 31 day period.

In connection with the results obtained by Leake and Evans,[4] by McCann,[5] and by the Minot-Murphy treatment, these cases appear of interest.

4075

The Digestion of Oils by Amoeba dubia.

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From the Zoological Laboratory, Harvard University.

The following account deals with experiments consisting of injection of various oils in one of the large free-living amoebae *(Amoeba dubia)*.[1] Injection was accomplished with a Chambers micro-manipulator. The experimental amoebae were from a race which has been cultivated by one of the authors for 4 years. Thus a minimum of variability has been ensured in the amoeba protoplasm concerned. Selected individuals were isolated and injected in the usual hanging drop. They were transferred singly to depression culture dishes. The diameter of the injected oil drop was measured by a calibrated ocular micrometer. These measurements were taken daily until droplet was either extruded or completely digested. Where extruded it was invariably located in the culture medium and measured for decrease in volume. Both experimental and control animals were placed in non-toxic distilled water from the same source as that used for the mass culture of the amoebae.

Nine representative oils were used: animal, vegetable and mineral, which were chosen with reference to their suitability for this type of microinjection. All of these oils were injected in the natural condition and 4 were also injected after radiation by an ultra violet lamp (mercury arc) for 20 minutes at a distance of 24 inches. The amount of digestion accomplished in the various oils is expressed in cubic micra. The average volume of an amoeba was determined by the following method: An amoeba crawling normally was regarded as a thin cylinder. The area was computed from camera lucida drawings, at appropriate magnifications, of 20 typical amoebae. A polar planimeter was used in making the computation. The thickness of the amoeba was measured directly by placing crawling amoebae on a coverslip and viewing the animals edgeways. By this means the volume of an amoeba was found to be approximately 500,000μ^3. The injected oil was considered as a sphere and the different volumes computed from the measurement of the diameter. The following table summarizes the results of the injection of this series of oils in *Amoeba dubia:*

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[4] Leake, C. D., and Evans, J. S., *Am. J. Med. Sc.*, 1924, clxviii, 819.

[5] McCann, W. S., PROC. SOC. EXP. BIOL. AND MED., 1928, xxv, 255.

[1] Schaeffer, A. A., *Arch. f. Protistenk.*, 1916, xxxvii, 204.

TABLE I.

Oil	No. amoebae injected	No. amoebae digesting oil	Aver. total vol. in μ^3 digested per amoeba	Ave. vol.dig. / Ave. vol. am.	No. days injected amoebae lived	No. days control amoebae lived
Codliver (nonradiated)	30	15	41,300	8.3%	6.	4 to 5
Codliver (radiated)	32	6	26,900	5.4%	4.5	4.5
Olive (nonradiated)	20	14	40,800	8.2%	5.5	5.
Olive (radiated)	29	24	11,700	2.3%	5.	5.
Cottonseed (nonradiated)	23	16	20,300	4.0%	6.	6.
Cottonseed (radiated)	12	6	13,400	2.6%	3.	6.
Linseed (nonradiated)	11	0	0	0.	5.	5.
Linseed (radiated)	16	4	8,300	1.7%	5.	5.
Sperm (nonradiated)	32	21	17,500	3.5%	7.	5.
Peanut (nonradiated)	19	9	6,900	1.4%	3.5	4.
Nujol	12	0	0	0.	4.5	4.5
Oleic acid	20	0	0	0.	4.5	4.5
Oxfoot	18	0	0	0.	4.5	4.5

The relative digestibility of these oils by *Amoeba dubia* may be summarized as follows:

1. Codliver (nonradiated).
2. Olive (nonradiated).
3. Codliver (radiated).
4. Cottonseed (radiated).
5. Sperm (nonradiated).
6. Cottonseed (radiated).
7. Olive (radiated).
8. Linseed (radiated).
9. Peanut (nonradiated).
10. Linseed (nonradiated).

It appears that radiation with the ultra violet rays had a retarding effect on digestion of the oils so treated, with the single exception of linseed oil. At present we propose no explanation for this phenomenon.

The operation of injection of oil is accomplished without injury to the amoeba unless the amount injected much exceeds 225,000 μ^3. When this amount of oil is injected experience has shown that the amoeba rapidly becomes sluggish, tends to round off and dies usually in 24 to 48 hours. It was found by experience that the volume of injected oil to give best results varied between volumes from about 14,000 μ^3 to about 65,000 μ^3 In volumes below 225,000μ^3 the oil droplet was received and carried about in the endoplasm apparently in the same manner as other free-moving contained particles. An amoeba injected with an optimum volume of oil does not differ essentially in appearance, when examined soon after the injection, from a control animal and its behavior in regard to endoplasmic streaming, locomotion, etc., is strikingly similar to that of the typical control amoeba. As can be seen in Table I there is no significant difference between the total length of life of control and injected animals. In the case of nonradiated olive oil, nonradiated codliver oil and nonradiated sperm oil there is an increase in the length of life of the injected amoeba over the control.

As measurements of the oil droplets contained by the amoebas showed a decrease in diameter indicating a gradual breaking down of the oil the endoplasm correspondingly became increasingly filled with brownish particles which imparted a characteristic granular appearance to the amoeba. Such amoebae were recognizable at a glance from those which had extruded the oil without any digestion or from the control animals. Both the granular appearance and the color gradually disappeared during the course of the experiment.

Digestion did not take place in every case of injection, even with those oils in which the greatest total amount of digestion occurred

(*Cf.* Table I). The number injected represents amoebae which retained the oil for the period between injection and isolation with subsequent measurement. This period varied from 20 minutes to 2 hours.

The 3 oils last considered in Table I are similar in the respect that no digestion whatever took place. In the case of the mineral oil, nujol, none was expected. Injection of this oil was made at the beginning of the experiment to note the reaction, if any, of amoeba protoplasm to an inert fluid. When oleic acid was injected a very rapid and peculiar response followed—the oil was almost immediately surrounded by an envelope of apparently coagulated endoplasm and was extruded in times varying from 45 seconds to 3 to 8 minutes. A similar phenomenon was observed after injection of ox-foot oil but at a slower rate. (5 minutes to a few hours.)

As a result of this work definite evidence is presented that the protoplasm of *Amoeba dubia* has the ability to digest oils and therefore the presence of a lipolytic substance in this protoplasm is hereby demonstrated.

4076

Cocaine Potentiation of Epinephrine and Ephedrine Action on Uterus and Intestine.

C. H. THIENES AND A. J. HOCKETT.

From the Department of Pharmacology, University of Oregon Medical School.

The work of Froehlich and Loewi[1] demonstrating that cocaine increases the sensitivity to epinephrine of the iris, urinary bladder, salivary glands and blood vessels of the cat, followed by De Eds'[2] results showing antagonism by cocaine of the pressor action of ephedrine, suggested the need for work with these drugs on other organs.

With excised strips of non-gravid uterus of the rabbit, suspended in Tyrode solution, there was a definite (20-400%) potentiation of epinephrine and ephedrine actions by cocaine. The cocaine-ephedrine potentiation was evident also on the ergotaminized rabbit uterus, no longer responsive to epinephrine, and on guinea pig uterus. Ephedrine caused contraction of both organs. These facts are important in the analysis of the site of action of ephedrine, and possibly also of the sensitizing action of cocaine.

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[1] Froehlich and Loewi, *Arch. Exp. Path. Pharm.*, 1910, lxii, 159.

[2] De Eds, PROC. SOC. EXP. BIOL. AND MED., 1927, xxiv, 551.

It is to be noted that the above potentiations were upon organs contracted by epinephrine or ephedrine. Reports by Lindblom[3] and Halsey[4] indicated a similar cocaine sensitization of the small bowel to the inhibitory action of epinephrine. We, however, have made 15 trials in 8 animals, without being able to demonstrate any definite sensitization of the small bowel of the rabbit or the small or large bowel of the guinea pig toward either epinephrine or ephedrine. The more frequent finding was an antagonism of the inhibitory action of epinephrine or ephedrine by cocaine.

No change in pH resulted from adding the cocaine solution to the organ bath, hence pH changes could not account for the sensitization.

4077

Relation of Bone Development in Infants to Calcium and Phosphorus Retention Ratios.

AMY L. DANIELS AND MARY K. HUTTON.*

From the Iowa Child Welfare Research Station, State University of Iowa.

Calcium and phosphorus retentions in infants receiving 3 different types of cow's milk modifications have been determined. In 2 cases the infants, who were quite normal, received the particular modifications, namely boiled cow's milk, and dried milk† for several consecutive months during the first year, thus making possible a number of metabolism studies on the same infant. With the 3rd mixture, namely S. M. A.,‡ the food was given from one to 2 weeks before the metabolic period, 2 studies being made with one infant; and one with a 2nd infant. The calcium and phosphorus retentions in one rachitic child have been included for comparison. Cod liver oil and orange juice were given daily in all but one case. In this,

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[3] Lindblom, *Compt. Rend. Soc. Biol.*, 1926, xcv, 1072.

[4] Halsey, personal communication.

* This study was made possible through the courtesy of the Department of Pediatrics, College of Medicine of the State University of Iowa.

† Klim: A whole dried milk preparation manufactured by Merrill Soule and Company, Syracuse, New York.

‡ S. M. A.: A cow's milk preparation in which the fat has been so modified as to more nearly resemble that of human milk. Cod liver oil is included in its preparation.

TABLE I—*Calcium and Phosphorus Retention in Infants.*

Name	Age	Weight	Creatinin	Calcium.				Phosphorus.				Retention Ratio	Cod Liver Oil
				Ingestion	Excretion.		Retention per kg.	Ingestion	Excretion.		Retention per kg.		
					Urine	Feces			Urine	Feces			
A. Boiled Milk with Cod Liver Oil.													
	mo. da.	kg.	mg.	gm.	gm.	gm.	gm.	gm.	gm.	gm.	gm.	Ca:P	
E. M.	2—13	5.65	66	.793	.031	.383	.066	.628	.361	.065	.036	1.8	5
”	2—24	6.07	69	.793	.029	.508	.042	.628	.354	.104	.028	1.5	5
”	3— 9	6.57	72	.793	.039	535	.034	.628	.343	.132	.023	1.4	5
”	3—24	6.97	83	.866	.043	.673	.021	.676	376	.179	.013	1.7	5
”	4— 6	7.25	85	.866	.037	.626	.028	.676	376	.164	.019	1.5	5
”	4—13	7.47	91	.938	.048	.685	.027	.738	.449	.180	.015	1.8	5
B. Dried Milk with Cod Liver Oil.													
P. H.	5	8.50	108	1.092	.038	.781	.032	.917	.526	.240	.018	1.8	5
”	5—15	8.88	112	1.092	.036	.759	.033	.917	.491	.279	.017	2.0	5
”	5—26	9.30	116	1.092	.035	.754	.033	.917	.476	.296	.016	2.0	5
”	6—26	9.68	110	1.092*	.029	.821	.025	.917	.508	.291	.012	2.0	5
”	7— 3	9.87	120	1.092	.056	.844	.019	.917	.508	.282	.013	1.5	5

*Milk irradiated with mercury quartz lamp one hour at distance of two feet.

TABLE II—*Calcium and Phosphorus Retention in Infants.*

C. S. M. A. with Cod Liver Oil.

Name	Age	Weight	Creatinin	Calcium.				Phosphorus.				Retention Ratio	Cod Liver Oil
				Ingestion	Excretion.		Retention per kg	Ingestion	Excretion.		Retention per kg.		
					Urine	Feces			Urine	Feces			
	mo. da.	kg.	mg.	gm.	gm.	gm.	gm.	gm.	gm.	gm.	gm.	Ca:P	
M. E.	3—21	5.85	71	.447	.033	.303	.019	.335	.245	.046	.007	2.5	5*
J. M.	3—1	5.98	67	.467	.018	.392	.009	.368	.333	.037	—.0002		5
J. M.	5—21	7.87	77	.467	.025	.391	.006	.368	.292	.059	.002	3.0	5

*5 cc. prior to metabolism period.

D. Rachitic Child (Boiled Milk).

	yr. mo.												
D. W.	2—7	6.76	56	.978	.017	.979	—.003	.814	.183	.587	.006	Neg.	

Blood calcium—8.5 mg. Blood phosphorus—1.3 mg.

the oil, which previously had been given daily, was discontinued 10 days before the metabolism period.

Roentgenograms of the epiphyses and long bones of the 2 infants receiving the boiled and dried milk modifications were taken once a month. These indicated that normal calcification was taking place. Roentgenograms of a 9½ months old baby, an outpatient in our clinic, who had received only S. M. A. since he was 2 weeks of age, also showed normal calcification. This baby had received orange juice but no added cod liver oil.

The results of the investigation suggest that normal calcification of the skeleton takes place when conditions are such that the calcium and phosphorus are retained in the proportion of approximately 2 parts of calcium to one part of phosphorus. (Tables I and II.) The results further suggest that normal bone formation can take place at different levels of calcium and phosphorus retentions. With the exception of the rachitic child, the amount of calcium and phosphorus retained on the S. M. A. feedings was much less than on either the dried or boiled milk modifications, and yet normal calcification had taken place in all cases. The results on the S. M. A. are in accord with those of Gerstenberger and Nourse.[1] The size of the skeleton may depend on the amount of the calcium and phosphorus retained. Rickets would seem to be the result of the retention of a disproportion of calcium and phosphorus. The rachitic child retained the same amount of phosphorus as Baby M. E., who was receiving S. M. A. He was, however, in negative calcium balance; whereas Baby M. E. was retaining 2½ times as much calcium as phosphorus. These data, together with others to be reported later, suggest that the disproportion in the calcium and phosphorus retentions observed in rachitic infants receiving cow's milk modifications is due primarily to a faulty calcium metabolism, the metabolic disturbance being related to a deficiency of Vitamin D.

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[1] Gerstenberger and Nourse, *J. Am. Med. Assn.*, 1926, lxxxvii, 1108.

Missouri Branch.

Washington University School of Medicine, May 16, 1928.

4078

Studies on Homoio Transplantation of Skin Flaps.

PHINEAS RABINOVITCH. (Introduced by W. D. Collier.)

From the Department of Surgery, St. Louis University School of Medicine.

It has been our aim in this work: (1) To study the development of circulation in homoio transplantation of skin flaps, and (2) to determine the fate of the flap when the circulation has been established.

Guinea pigs were used for our experiments. Skin flaps 2½" x 1½" were raised from flank and lateral wall of chest of one animal (Animal A) and applied to defect on back of other animal (Animal B). Entire thickness of skin was used. A flap thus applied from animal A would receive its blood supply from animal A until vascular communications had been established with B. The 2 animals were kept together, strapped with adhesive. At 24-hour intervals, for 14 days, animals were killed and sections including flap, adjoining skin, and underlying tissues of B, were removed for microscopic examination. Three such series of experiments were followed. Related and unrelated animals were used, and blood matching was done, before and after operation.

The microscopic examination of the tissues at different stages of union reveals the following: Immediately after the flap was placed upon its new bed, a fibrin network is formed which seals it in place, and later by contraction, pulls the 2 raw surfaces together. After 24 hours, granulations begin to sprout out from the host and invade the flap, and are associated with moderate leucocytic infiltration. The flap produces a much less active reaction. By the 4th day there is complete absorption of fibrin and hemorrhage, and complete granulation healing of the line of suture. Different animals show variations in union and in reaction, but in all sections complete union is seen on beginning of the 5th day. From 4 to 8 days both host and flap show healthy tissues and granulation, and capillaries are seen communicating between host and flap. On the 9th and 10th day (sometimes the 8th) overlying epithelium of the flap shows desquamation of its superficial layers, in some places even to the degree of complete erosion of its surface. Collagen fibers lose their identity on the side of the flap. This tissue becomes edematous, infiltrated with leucocytes and shows capillary hemorrhages particularly along the line of fusion. The vessels from the host to the flap still show anatomical continuity, but do show hemorrhagic exudation. After we have determined the exact length of time it takes for complete establishment of circulation we next decided to study the progress of the flap, after separation of the animals, at the end of 1 to 2 weeks. It was noted that while the animals were united, one of the animals showed progressive emaciation, anemia and weakness, beginning about the 6th or 7th day, and usually one of them died if not separated. Death of the other animal sometimes followed several days later.

In all our experiments, although complete circulation has been established in the transplanted flap, death of the flap seems to take place sooner or later in one of 2 ways: Either by drying or crumpling of the graft or acute moist gangrene. When B is stronger than A the flap dies by acute moist gangrene. This happens on the 1st or 2nd day after separation, but when B was the weaker, the flap appeared normal for from 6 to 16 days. Then, however, the following changes were noted. At first the edges became cyanosed, the borders curl up toward the center, the entire flap is gradually converted into a dry, rough, elevated mass, and then cast off, usually completing the process of separation of dead from living tissue in 6 days. Animal B very often died later, but when alive it never brought about a strong reaction at the point of transplantation. After separation of the animals, if B were the weaker, it showed increasing appetite, became stronger, and then threw off the flap with greater reaction, moist gangrene.

It is evident that there are factors other than vascularization on which the vitality of the flap depends. The higher the organism is developed the more complicated are its cells and the more difficult it is to overcome its biological and biochemical peculiarities. Variations in conditions of existence, especially variations of biological and biochemical peculiarities, and dissimilar function between the cells of the flap and the host determine the fate of the transplanted tissue.

4079

Variability in Distribution of Allergic Skin Response.

H. L. ALEXANDER.

From the Department of Medicine, Washington University, St. Louis, Mo.

Allergy is used here in the meaning of human hypersensitiveness, clinical expressions of which are bronchial asthma, hay fever and urticaria. In these conditions, the most important diagnostic procedure is the skin test. Measured amounts of the foreign substance (allergen) to which an individual is suspected of being allergic, are injected into the superficial cells of the skin. A positive skin reaction represents the effect of contact between the injected allergen and a reacting substance, presumably an antibody, in the skin cells. The result of this contact is the elaboration of some stimulus that causes a local capillary permeability with consequent wheal formation.

It was observed, occasionally, that individuals who gave pronounced positive skin reactions at one time would give smaller or no reactions subsequently, and other individuals giving no skin response would occasionally develop a positive reaction at a later time. These patients had received no specific treatment and the technical features of the tests were kept constant. This variability was studied and forms the subject of this investigation.

It was found that when a given amount of allergen (0.02 cc.) is injected successively at various sites in the skin, there is a marked variation in the size of the resulting wheals. (Figs. 1 and 2.) For instance, the response on the back may be 2 or 3 times larger than that on the leg. There is no constant anatomical factor, although reactions on the back and abdomen tend to be larger than elsewhere.

These variations may be explained in one of 2 ways: (a) either throughout the skin cells, there is an uneven distribution of antibody to react with the constant amount of allergen injected at the various sites; or, (b) the capillary response which results from the reaction between allergen and antibody is not a uniform one.

Advantage was taken of the fact that histamin is known to produce wheals in dogs, similar histologically to those of human urticarial wheals. Consequently, 0.02 cc. of a 1 to 1000 histamin solution was injected into the skin of the abdomen, thigh and ear of dogs. The resulting capillary response was very uneven (Fig. 3). Here, there is no question of immune bodies.

From the analogy of the above reactions to histamin, it is conceivable that the variations in allergic wheal formation in human skin are due to lack of uniform response on the part of the skin cap-

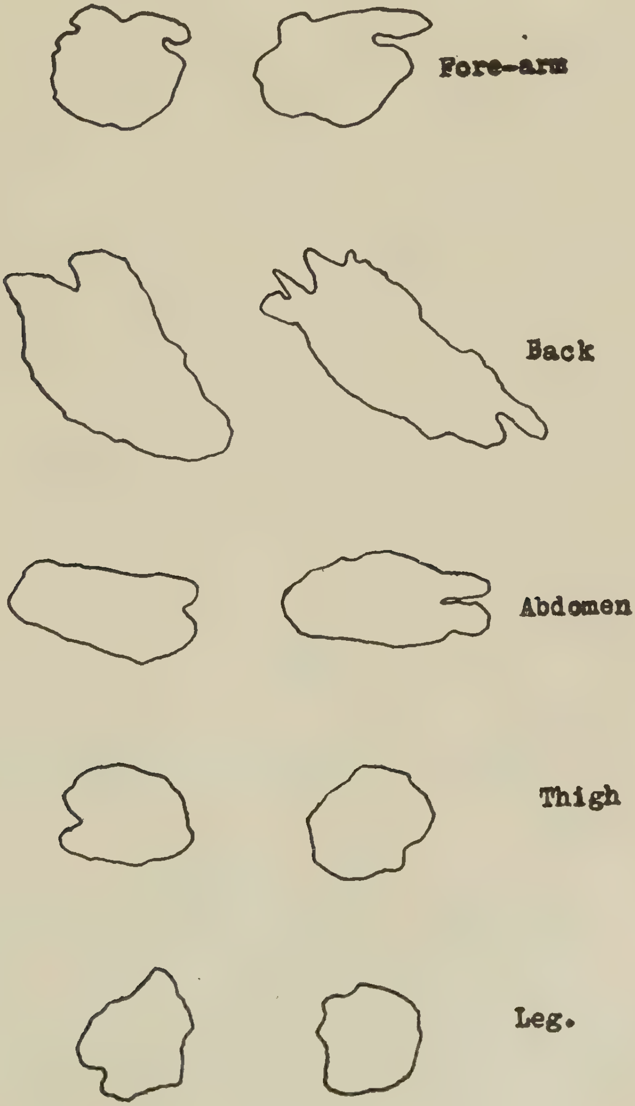

FIG. 1.

0.02 cc. of a 1 to 10,000 ragweed pollen extract injected into various sites of the skin of a hayfever patient.

illaries to the same stimulus, rather than to an uneven distribution of antibodies in the skin cells. These results suggest an explanation of the clinical phenomenon that urticaria, which is usually an aller-

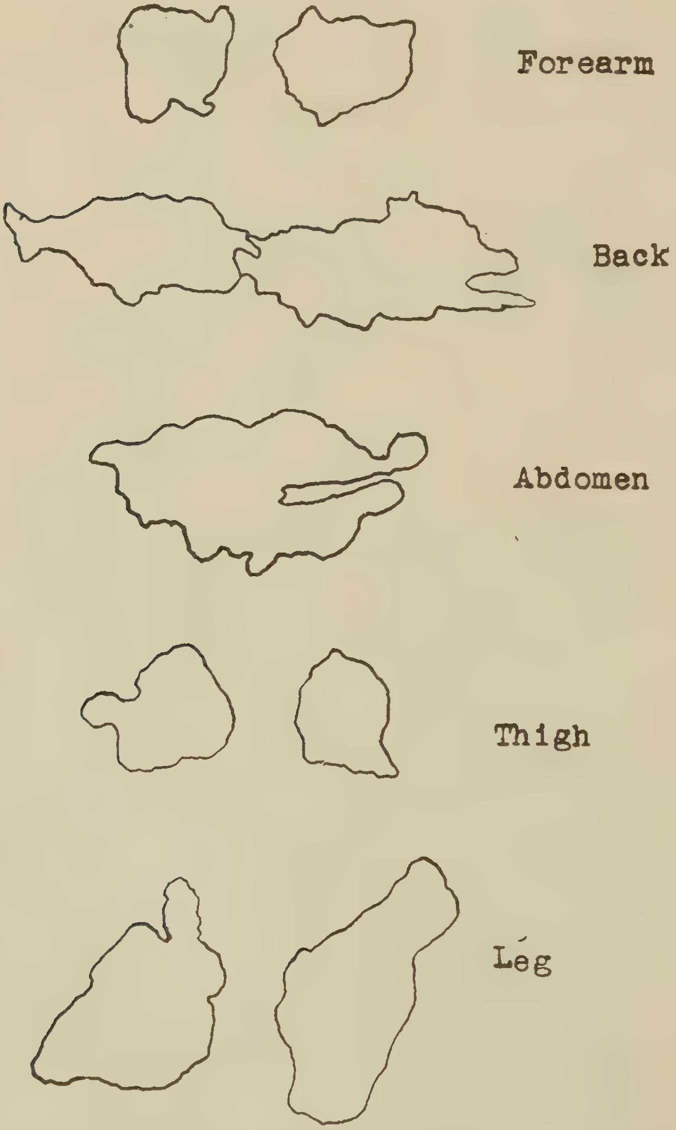

FIG. 2.

0.02 cc. of a 1 to 1,000 timothy pollen extract injected into various sites of the skin of a hayfever patient.

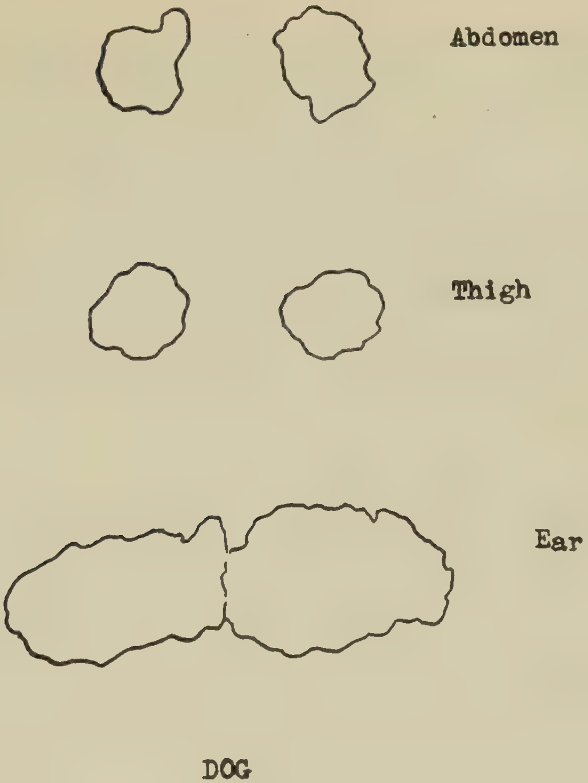

FIG. 3.
0.02 cc. of a 1 to 1,000 histamin solution injected into various sites of the skin of a dog.

gic manifestation, occurs as wheals of varying size, irregularly distributed throughout the skin.

4080

Observations on the Circulation of Guinea Pigs During Bronchospasm.

FRANCIS SMITH, J. S. HARTER AND H. L. ALEXANDER.

From the Department of Medicine, Washington University, St. Louis.

The purpose of this experiment is to study the effect of bronchospasm on the circulation with reference to filling of the right heart.

Since anaphylactic shock in guinea pigs is manifested by bronchospasm, these animals were chosen.

The technic of the experiment was as follows:

Guinea pigs of 700 to 1000 gm. were sensitized by an intraperitoneal injection of 3 to 5 cc. of a 1 to 2 solution of egg white in buffered saline solution. The animals were allowed 15 to 20 days to become sensitive. At the end of this time the animals were anesthetized with amytal.

A cannula was placed in the right subclavian vein and pushed down into the right auricle. This cannula was connected to a water manometer fitted with a recording float similar to that used in mercury manometers. Physiological saline containing 0.7% of heparin was used in this system to prevent clotting of the blood.

Another cannula was placed in the trachea and connected to a closed breathing system which in turn was connected to a tambour so as to show exchange of air during respiration. This system was hooked up just previous to giving the shocking dose.

A trochar connected to a tambour was placed in the pleural cavity. This did not disturb the intrapleural pressure since the closed system remained intact. The tambour was standardized on the record in order to transpose the readings to cm. of water pressure.

These pressures were all recorded on a kymograph simultaneously; so that a composite record was obtained.

After everything was set, the drum was run long enough to record normal pressures. One cc. of the egg white was then injected into the venous cannula and washed into the circulation with the saline heparin mixture.

With this method we hoped to show the effect of bronchospasm on the circulation. In order to demonstrate the effects of bronchospasm on the circulation 3 separate pressures were taken and a 4th calculated. These pressures are the intra-auricular, intrapleural, and arterial pressures. Effective venous pressure was calculated as the algebraic difference between the geometric mean of the intrapleural pressure and of the intra-auricular pressure and was taken to indicate the degree of filling of the right heart.* Also, measurements were made to show whether air was entering or leaving the chest. This measurement is designated on the records and graphs as vorlage.

Figure 1 is a graph which is an exact transposition of one of the records. The figures on the abscissa represent the time in seconds.

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* It is recognized that calculations of effective venous pressure will vary, depending upon the places where the venous measurements are made, and also upon the phases of the heart cycle. The effective pressures here recorded are mean pressures and were calculated according to the formula of Wiggers.[1]

[1] Wiggers, C. J., "Circulation in Health and Disease," Philadelphia, 1923, 105.

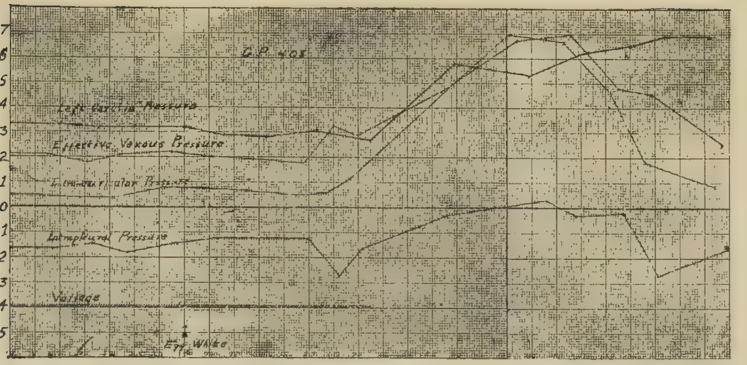

FIG. 1.

The figures on the ordinates represent the pressures in cm. of water above or below the zero except in the carotid pressure which is in cm. of mercury. The point at which egg white was injected is indicated. The vorlage indicates exchange of air up to the end of the marks.

In all the graphs intrapleural pressure is seen to fall either markedly, moderately, or very slightly; the fall being followed by a rise.

In all cases the effective venous pressure rose soon after the injection of the egg white; especially so in the cases where the bronchospasm was fatal to the guinea pig. At times, the effective venous pressure rose only slightly, the usual changes in intrapleural and intramuscular pressures being only slight. (Fig. 2.) In these cases,

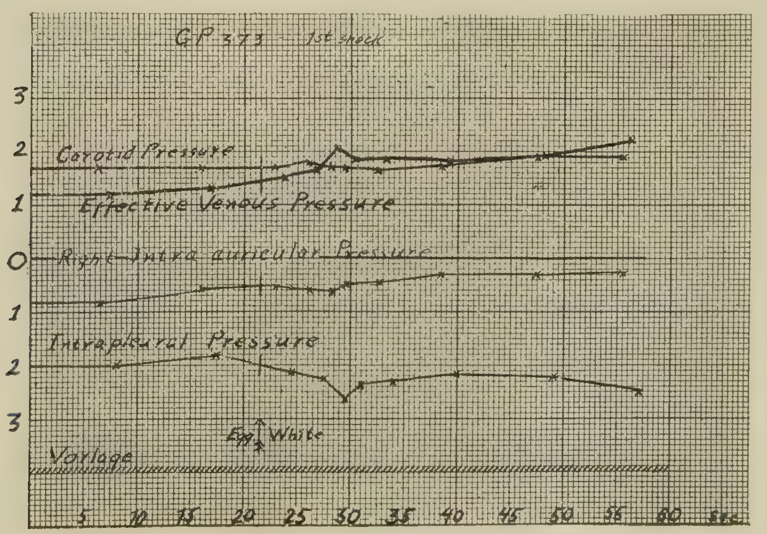

FIG. 2.

the guinea pigs continued to get air in and out of the lungs during the whole experiment and did not die because of bronchospasm.

Carotid pressure rose in varying degrees after the onset of bronchospasm.

Conclusions. 1. The circulatory effects as a result of bronchospasm were studied, particularly with reference to the effective venous pressure. 2. When bronchospasm is extreme there is a marked increase in the effective venous pressure. 3. When bronchospasm is not extreme there is very little change in the effective venous pressure.

4081

Extraction of Ovarian Hormone From Urine.

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Since the discovery of the presence of the ovarian hormone in the blood (Loewe,[1] Frank[2]) and in urine (Loewe[3]), Ascheim and Zondek[4] have shown that the urines of pregnant women contain large quantities of the hormone. This finding, which has been confirmed by Laqueur,[5] Slotta[6] and others, is of exceptional value in that it provides an excellent source of the hormone from the standpoint of expense as well as availability.

Recently Zondek[7] has published a preliminary note in which he states that the common organic solvents may be used to extract the hormone. We have used several organic solvents in addition to those commonly used but have found none so satisfactory as ethyl ether. In Table I are the data obtained by 4 successive extractions of the urine with ¼ its volume of ethyl ether. The combined ethereal extracts were washed with dilute alkali and dilute acid and then distilled to dryness. The residue was taken up in hot alcohol, cooled, filtered, and the potency determined. The data of Table I indicate that this very simple procedure gives a product of considerable activity.

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[1] Loewe, S., *Klin. Wochenschr.*, 1925, iv, 1407.

[2] Frank, R. T., and Goldberger, M. A., *J. Am. Med. Assn.*, 1926, lxxxvi, 1686.

[3] Loewe, S., and Lange, F., *Klin. Wochenschr.*, 1926, v, 1038.

[4] Aschheim, S., and Zondek, B., *Klin. Wochenschr.*, 1927, vi, 1322.

[5] Laqueur, E., Dingemanse, E., Hart, P. C., and deJongh, S. E., *Klin. Wochenschr.*, 1927, vi, 1859.

[6] Slotta, K. H., *Deut. Med. Wochenschr.*, 1927, liii, 2158.

[7] Zondek, B., *Klin. Wochenschr.*, 1928, vii, 485.

TABLE I.

Ovarian Hormone of Urines Obtained Just Prior to Delivery.

Rat units per liter	480	500	630	710	625	830	1000	470	1240
Wt. of 1 R. U. in mg.	—	0.06	0.06	0.12	—	0.06	0.14	0.22	0.06

Owing to the danger of oxidation of the hormone by the peroxides of ethyl ether, we have made use of an alternative method which has the additional advantage of being less time-consuming. The principle involved is the familiar continuous liquid extraction of a solution but the procedure is so modified that the liquid being extracted siphons into the apparatus at the top and the spent liquid is removed at the lower end by the pressure of the column of urine and chloroform. By properly regulating the speed of ingress of the urine and the rate of boiling of the chloroform, several gallons may be run through the apparatus with practically no attention but with almost complete recovery of the hormone from the urine. The chloroform extract is washed with dilute alkali and acid and distilled. The residue which is taken up in alcohol furnishes the stock from which aqueous solutions are prepared which are considerably more refined than the alcoholic solutions.

The aqueous solutions may be purified still further by the use of organic solvents. Properly prepared extracts exhibit an activity only slightly less than that of preparations from the liquor folliculi (1000 R. U. or more per 1 mg.). This, coupled with the behavior during the course of preparation and the resemblance in physiological response, leads us to the belief that the substance extracted from the urine may be chemically identical with the ovarian hormone.

In Table II, we present data upon the activity of extracts prepared from single samples of post-partum urines collected by the nurses of a maternity ward. While our data are far from complete, they seem to indicate rather clearly that the kidney ceases to eliminate the hormone soon after delivery. This would lead one to suspect that the concentration in the blood has diminished and that the organ responsible for the production of the hormone has ceased to function in that respect.

TABLE II.

Ovarian Hormone in Post-Partum Urines.

Hours Post-Partum	8½	37	48	72	96	144	192	264
Rat Units per liter	640	500	80	22	20	<5	<5	<4

4082

Peripheral Distribution of Myelinated Nerve Fibers Through Gray Communicating Rami in Dog.

ALBERT KUNTZ AND D. IVAN FARNSWORTH.

From the St. Louis University School of Medicine.

The cervical, lower lumbar (below L. II) and sacral spinal nerves are connected with the sympathetic trunk only through gray communicating rami which, according to the current teaching, comprise no spinal nerve components, but only fibers of sympathetic origin. Certain clinical and experimental data strongly suggest that the gray communicating rami joining the brachial and lumbosacral plexuses also comprise afferent fibers of spinal ganglion origin.

To test this hypothesis, the following experiments were carried out. Two series of dogs were subjected to operation. In the first series both roots of the thoracic spinal nerves from the 1st to the 8th inclusive were cut unilaterally just distal to the spinal ganglion, leaving the communicating rami intact. In some of the animals in the 2nd series both roots of the lumbar nerves, usually from the 1st to the 6th inclusive, were cut unilaterally distal to the spinal ganglia, in the others the left lumbar sympathetic trunk was resected above the level of the communicating ramus of the 6th lumbar nerve. The animals were killed 2 to 5 weeks after operation, when the communicating rami connecting the stellate ganglion with the cervical and first thoracic nerves, in the first series, and the communicating rami joining the 6th and 7th lumbar and 1st sacral nerves, in the 2nd series, were removed bilaterally, fixed in osmic acid and examined for myelinated fibers.

In every case the number of myelinated fibers in the corresponding rami was less on the side of the operation than on the opposite side. The results in the following cases are typical of the results obtained in both series.

		Number of myelinated fibers	
Operation	*Rami examined*	*Left*	*Right*
Case 1. Both roots of upper 8 left thoracic nerves cut.	Stellate ganglion to cervical nerves.	8	87
	Stellate ganglion to 1st thoracic nerve.	15	166
	Total	23	253

Case 3. Both roots of upper 6 left lumbar nerves cut.	Gray ramus of L. VI.	12	42
	Gray ramus of L. VII.	0	0
	Gray ramus of S. I.	0	6
	Total	12	48

Inasmuch as the preganglionic components of the efferent chains involved in the sympathetic innervation of the peripheral blood vessels and other tissues in the area of distribution of the somatic rami of the spinal nerves terminate in the ganglia of the sympathetic trunk, any fibers which join the spinal nerves through the gray rami, except those of sympathetic origin, must be regarded as fibers of spinal ganglion origin. The animals used in this study were young dogs whose gray rami contain relatively few myelinated fibers. Consequently, the myelinated fibers present were easily counted. The difference between the number of myelinated fibers in the corresponding gray rami on the normal and operated sides represents the number of myelinated posterior root fibers present. This number need not be regarded as representing the total number of fibers of spinal ganglion origin in the gray rami in question, since many posterior root fibers are unmyelinated.

The posterior root fibers which join the brachial plexus, through the gray rami arising from the stellate ganglion are components of the thoracic nerves, and probably belong to the same segments as the preganglionic components of the efferent chains with which they are associated functionally. Those which join the lumbosacral plexus, through the gray rami of the lower lumbar and sacral nerves, are components of the lower thoracic and upper lumbar nerves, and probably belong to the same segments as the preganglionic components of the efferent chains involved in the sympathetic innervation of the lower extremity.

4083

Heredity and Internal Secretion on Origin of Mammary Cancer in Mice.

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From the Department of Pathology, Washington University School of Medicine, St. Louis, Mo.

More than 20 years ago Loeb in preliminary investigations on the heredity of cancer in mice first applied to the analysis of this problem a method which allowed the establishment of the significance of heredity in mice on a much more secure basis than was possible by the use of the statistical methods similar to those employed in the study of the influence of heredity in human cancer. This method consisted in the breeding of separate families and strains of mice in the same breeding establishment and in the study of the cancer rate in successive generations of strains which had thus been kept under similar conditions as far as the outer environment was concerned. By this method he found in cooperation with Miss Lathrop that heredity was a factor of very great significance in the origin of cancer of mice.[1] While certain strains had a cancer rate approaching zero, other families had a rate approaching 80% or more. In successive generations these differences between different strains remained approximately constant.

However, in the further analysis of the causes of mammary cancer in mice we found that in addition to heredity, the functional activity of the sex organs played a significant part in the origin of cancer of mice. We found that the prevention of mice from breeding lowered the cancer rate definitely and that in different strains the effect of the prevention of breeding differed in intensity. However, we found castration of the mice to be of even greater significance and moreover the effect of castration was the greater, the earlier the ovaries were removed. A quantitative relation was thus established between the internal secretion of the ovary and the frequency with which cancer appeared in the breast of mice. The growth stimuli emanating from the ovary and affecting rhythmically the mammary gland acted thus in a similar quantitative manner to tar, which when applied experimentally to the skin also produced cancer the more frequently and the earlier, the earlier and oftener the tar had been used. In both cases, cancer would develop a long time after these 2 types of stimuli had ceased to act. Stimuli developing in the outer and inner environment acted therefore in a similar manner in the causation of cancer. These latter investigations were subsequently confirmed and extended by Cori.[2]

As to the mode in which heredity leads to the development of mammary cancer in mice and through which mechanism it becomes potent, nothing definite is known at the present time. In view of the fact that in addition to the hereditary factor the functional activities of the sex organs greatly influence the incidence of cancer in mice, it is conceivable that the hereditary condition itself acts through hereditarily transmitted differences in the functional activity of the ovaries. If such a relation should exist, it should be possible to establish it by comparing the sexual periodicity in female mice belonging to strains with a very high cancer rate with the periodicity of the cycle in mice not belonging to such strains. We obtained through the kindness of Mr. M. C. Marsh of the State Institute for the Study of Malignant Diseases in Buffalo, female mice belonging to a strain in which the cancer rate exceeded 80%. In a number of these animals we studied the length of the oestrous cycle and found it to be on the average very similar to the cycle of ordinary white control mice in which, while the cancer rate had not been definitely established, it did not appear to be high. In the strain with a high cancer rate the length of the cycle was slightly greater than in the controls. The duration of the oestrous cycle in the tumor strain was likewise slightly greater than in the ordinary white mice previously studied by Allen.[3] In several of the mice in the high tumor strain cancers developed while under observation. We found that the appearance of the tumor did not greatly alter the length of the oestrous cycle. We furthermore had at our disposal through the kindness of Miss Clara J. Lynch from the Rockefeller Institute a strain of brown mice with a relatively low cancer incidence in animals kept from breeding. In these mice the sexual cycle was on the average longer than in the white mice belonging either to the ordinary strain or to the high tumor rate strain. This fact also corresponds to previous observations of Allen, who found in a strain of brown mice which he examined the length of the sexual cycle to be greater than in ordinary white mice.

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[1] Loeb, Leo, *Am. Naturalist*, 1921, lv, 510.

[2] Cori, C. F., *J. Exp. Med.*, 1921, xlv, 983.

On the basis of these studies of the sexual periodicity in mice, we may conclude that there is in all probability no definite relation between the length of the sexual cycle in these animals and the hereditary tendency to cancer, in the sense that mice with a higher cancer rate have a shorter sexual cycle, and we must therefore in all probability seek the point of attack of the hereditary factors not in the functional activity of the ovary but elsewhere. However, we consider these studies as preliminary and we hope to be able to continue them.

In conclusion we may point out that the fact that variable conditions in the inner environment of the animals greatly influence the incidence of cancer in addition to heredity, complicates the analysis of the genetic factors which determine the mode of hereditary transmission, and that in the study of cancer in hybrids we can not expect simple ratios under these circumstances.

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[3] Allen, E., *Am. J. Anatomy*, 1922, xxx, 297.

4084

Effect of Potassium Iodide on Proliferative Activity of Thyroid Gland in Guinea Pigs.

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From the Department of Pathology, Washington University School of Medicine, St. Louis, Mo.

In our investigations we attempted first, to determine in a quantitative manner the increase in mitotic activity which is caused in the thyroid of guinea-pigs fed with potassium iodide, and secondly, we intended to determine whether there was any relation between the quantity of KI and the proliferative activity in the acini. The experiments were carried out on 4 sets of guinea pigs weighing on the average between 350 and 450 gm.; some of these were fed with varying quantities of potassium iodide for different periods of time, while others were kept as controls. The first set of animals received a daily dose of 0.01 gm. KI, the second set 0.05 gm. KI, and the third set 0.1 gm. KI. The fourth set was kept as controls and did not receive any potassium iodide. The iodide was administered in the form of pills fed by mouth, great care being taken that all of the substance was swallowed. In different groups of animals the feeding was continued for periods of 10, 15, 18, 20 and 30 days respectively, and at the end of each period the animal was killed with chloroform, and both lobes of the thyroid excluding the isthmus were immediately removed after the death of the animal and at once fixed in Zenker's solution. The glands were cut in complete serial sections and stained with eosin and hematoxylin. The average number of sections obtained for every gland varied between 450 and 500; mitoses were counted in every tenth section in a very exact manner, the number of mitoses thus obtained was multiplied by 10 in order to find the total number of mitoses in the thyroid gland.

We may state that first, the administration of KI leads to an exceedingly pronounced increase in the proliferative activity of the thyroid gland. While in normal guinea pigs not fed with KI the average number of mitoses varied approximately between 100 and 200 in the whole gland, in the animals fed with KI the number may be as high as 8000 and quite commonly reached figures of 4000 and 5000. Secondly, we found that there is a definite relation between the amount of KI fed and the mitotic activity of the thyroid gland which results therefrom. The intensity of mitotic proliferation was smallest in the set fed with 0.01 gm. and was greatest in the set fed with 0.1 gm. KI; it was intermediate in the guinea pigs which received 0.05 gm. As to the activity of phagocytes we found it greatly increased in the thyroid glands of the animals fed with KI, and in consequence of this increased activity on the part of the phagocytes the softening of the colloid took place in some acini. Otherwise there was no striking difference found in the character of the acini, colloid and epithelium between the controls and the animals fed with potassium iodide. After feeding with KI through a period of 30 days, the mitotic activity has ceased altogether; this condition was associated with and probably caused by the taking up of fluid on the part of the colloid, which just increased in size and exerted pressure on the acini. As a result of this increased pressure the acini became larger, and the epithelium flattened out, and in other cases adjoining acini coalesced.

Minnesota Branch.

University of Minnesota, May 31, 1928.

4085

Rapid Stimulation of Hemoglobin Synthesis in Secondary Anemias After Feeding Fetal Calf's Liver.

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From the Medical Service of the University Hospital, Minneapolis, Minn.

Observations by different workers show that in patients afflicted with some form of secondary anemia there is as a rule no response to the feeding of calf's liver or of the Cohn-Minot liver extract. To the well known response of patients with pernicious anemia to this extract has recently been added the definite but peculiar type of response, which normal individuals show to the same extract. It is being assumed that the nature of the effect of the extract is to bring about a maturation or discharge into the circulation of erythrocytes or a combination of both these processes.

It is generally recognized that it is not the erythropoesis which is primarily at fault in socalled secondary anemia but the ability to synthesize enough hemoglobin to give the proper hemoglobin concentration in the erythrocytes that are being formed. The lack of effect of liver or liver extract upon secondary anemia is in harmony with this view.

The appearance of abundant amounts of hemoglobin already during the early stages of the development of the primitive erythrocyte was considered as a significant fact during our search for a way specifically to stimulate hemoglobin synthesis. The important rôle which the fetal liver takes in the next stage of erythropoesis led us to the attempts to be communicated in this paper.

We have adopted the feeding of fetal calf's liver as a mode of treatment of certain types of secondary anemia. Characteristic features of these anemias are their prevalence in women between the age of 25 and 45, marked chronicity and failure to respond to treatment with iron or chlorophyll-rich diet as well as to ordinary calf's liver or liver extract. The apparent lack of any causative agent makes these cases stand out more or less as primary or essential anemias of the type one hematologically characterizes as secondary. One of the curves in our charts represents a boy, age 10, with an almost aplastic anemia of secondary type. The other curves are from women of the type just indicated.

The livers, which have been used so far, have been from calf fetuses measuring 40 cm. or more from the tip of the nose to the ischial tuberosities. Recent therapeutic observations have led us to a somewhat different selection, the fetuses not to exceed 70 cm. in length and with a preference for the smaller ones. Microscopic sections of livers from fetuses of different length reveal in an 18 cm. embryo the blood forming islands almost as prevalent as the liver structure proper, in a 77 cm. fetus only a few islands of normoblasts and in a 112 cm. calf (full term) practically no signs of intrahepatic blood formation. The livers have been removed from the fetuses within 4 hours after the animals have been killed, ground through a meat chopper, dried in a hot air current, the material suspended about an inch above a hot plate, the dried material powdered and administered either as powder or made into tablets. The equivalent of about 300 g. of liver has been fed daily.

Chart 1 demonstrates in 4 representative cases the increase of hemoglobin during fetal liver feeding in percentage of the initial values, these having been calculated as unity. The actual hemoglobin values at the beginning and end of the experiment are

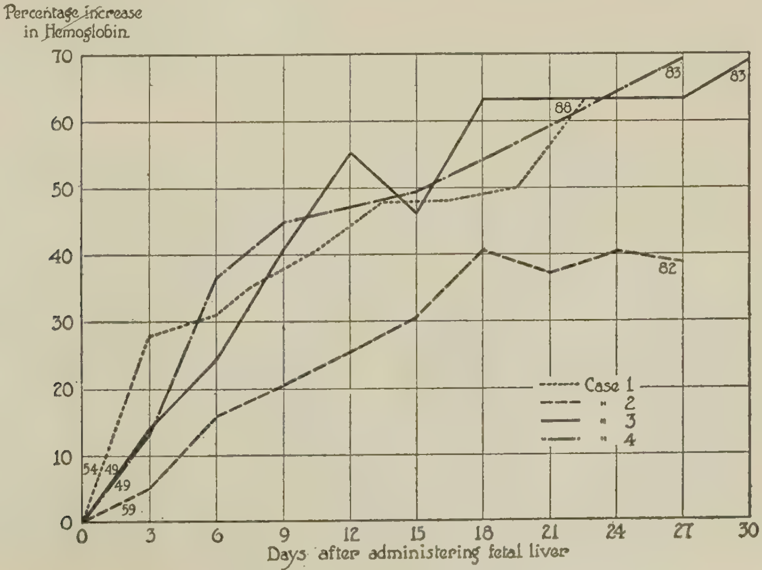

CHART 1.

attached to the individual curves. The hemoglobin values, determined according to Sahli against permanent standards have been read after 15 minutes, when the curve for the color development has

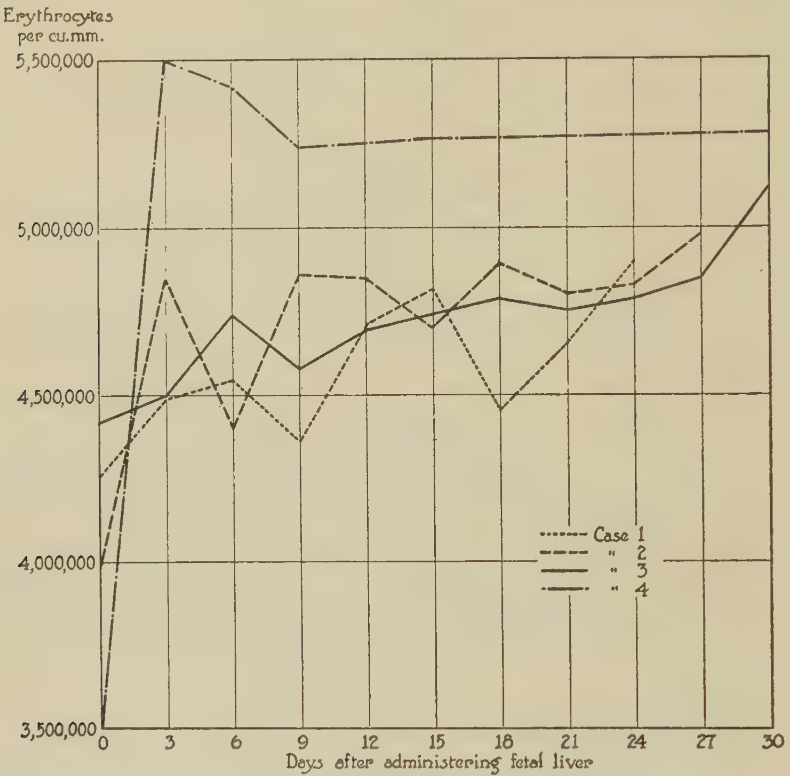

CHART 2.

flattened out, instead of after 2 minutes. Chart 2 gives the corresponding curves for the number of erythrocytes. Chart 1 shows in all cases a uniform increase in the hemoglobin content, in 3 of the 4 cases amounting to from 60% to 70% of the initial values within 22 to 30 days, and in all cases leading up to practically normal absolute figures. A comparison between Chart 1 and Chart 2 fails to reveal any correspondence between the curves for the number of erythrocytes and for hemoglobin content. Particularly elucidating are the curves labeled 4. Here a rapid discharge of hypochromatic erythrocytes brings the blood count to a high normal level, only slightly altering the hemoglobin content The hemoglobin curve then continues to rise, with the erythrocyte curve remaining level. As an approximately correct expression one might state that the time required to bring about a normal hemoglobin content in a hypochromatic type of anemia is the time required not only to raise the erythrocyte count to normal but to replace the erythrocytes present in the circulation at the onset of treatment with new erythrocytes of normal hemoglobin content. This is in fundamental contradistinction to the situation in pernicious anemia.

At no time during the treatment with fetal liver was there any increase in the number of reticulocytes.

Conclusion: A procedure to accelerate the hemoglobin synthesis in secondary anemia through the feeding of fetal calf's liver has been carried out successfully.

4086

Effect of Cholesterol Exposed to Roentgen Rays on Rachitic Rats.

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Hess and Weinstock[1] state that cholesterol, which has been irradiated with roentgen rays, does not cure rickets, and also that the absorption spectrum in the ultra violet of cholesterol is not changed by this kind of radiation. On the other hand, Reinhard and Buchwald[2] found that a definite change takes place in the absorption if cholesterol is irradiated in chloroform solution. This change in the absorption was similar to the change that is produced by irradiation with ultra violet. If commercial cholesterol is exposed for a short time to ultra violet radiation from a mercury arc, it obtains a curative effect on rickets and there seems to be a correlation between the activity and the change in the absorption. It seems, therefore, that cholesterol in a chloroform solution might obtain anti-rachitic properties by being exposed to roentgen radiation.

After some preliminary tests with the production of rickets in rats, the following experiment was carried out. Through the courtesy of Dr. Cornelia Kennedy a litter of 8 rats was obtained after weaning, at the age of 28 days. The mother rat had been fed on Steenbock's diet[3] which is poor in vitamine A. The eight rats were put on Steenbock and Nelson's diet No. 2966[4] free from vitamine

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[1] Hess, A. F., and Weinstock, M., *J. Biol. Chem.*, 1925, lxiv, 1923.

[2] Reinhard, M. C., and Buchwald, K. W., *J. Biol. Chem.*, 1927, lxxiii, 383.

[3] Steenbock, *Science*, 1923, lviii, 449.

[4] Nelson, E. M., and Steenbock, H., *Am. J. Physiol.*, 1925, lxxiii, 341.

D. Rats C and D were on this diet alone; A and B received 0.2 cc. of codliver oil per day; E and F received unirradiated cholesterol, and G and H received cholesterol which had been exposed to roentgen rays while dissolved in chloroform. The codliver oil was fed by means of a pipette. The cholesterol was administered by pouring 1 cc. of a solution of 0.6 gr. of Kahlbaum's cholesterol in 100 cc. chloroform on the day's ration and the chloroform evaporated off at room temperature. Any food remaining was added to the next ration.

The cholesterol solution to be irradiated was sealed in glass tubes about 15 cm. long and 1.5 cm. in diameter (15 cc. in each tube). As a rule, one tube at a time was placed inside the large metal cylinder that housed the roentgen tube and was left there until shortly before it was needed. The distance from the target to the center of the cholesterol container was 57 cm.; 180 to 200 kilovolts and 30 milliamperes were used, the only filter being the glass wall of the container. The time of exposure varied from 1 to 15 hours with interrupted radiation, the average time being 7 hours. The rats were kept 26 days, and at the end of this period roentgen pictures were taken which showed the typical rachitic picture in rats C to H inclusive. Sections were made of bones from all the rats, the frozen sections being made without decalcification and stained according to Von Kossa's technique with silver nitrate.[5] In rats C to H there was no evidence of calcification in the epiphyseal cartilage and in the greater part of the metaphysis. Both of these tests showed no difference in the intensity of the rickets produced in the last 6 rats. Rats A and B were normal in both of these tests. The results of the experiment are summarized in the following table:

TABLE I.

Rat	Addition to ration	Weight			Roentgen Plate	Calcium staining[5]
		1st day	14th day	26th day		
A	Codliver oil	59	72	82	—	—
B	” ”	44	60	70	—	—
C	———	57	72	78	+	+
D	———	56	71	75	+	+
E	Unirradiated Cholesterol	56	70	77	+	+
F	”	55	71	77	+	+
G	Irradiated Cholesterol	57	71	77	+	+
H	”	61	78	86	+	+

— = No evidence of rickets could be noticed.
+ = Definite evidence of rickets present.

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[5] Von Kossa, *Ziegler's Beitrage*, xxix, 190.

Our experiment thus shows that the roentgen radiation to which the solution of 0.6% cholesterol in chloroform was exposed did not induce any anti-rachitic potency to the cholesterol. The roentgen dose was neither exceedingly small nor exceedingly large. We therefore consider that enough change should have been produced to have had a noticeable effect on the rats if anti-rachitic properties were induced by irradiation with roentgen rays of a solution of cholesterol in chloroform, and doubt that the dose could have been large enough to both produce and destroy completely an antirachitic substance.

We wish to express our appreciation to Dr. Grace Medes for the advice received regarding the diet for the rats used in this experiment.

4087

A Streaming Potential Method of Measuring Electrokinetic Potentials of Proteins.

DAVID R. BRIGGS. (Introduced by R. A. Gortner.)

From the Division of Agricultural Biochemistry, University of Minnesota.

The sign and magnitude of the electrical charge on proteins has profound effects upon the physico-chemical properties of protein systems, and various methods have been utilized to evaluate these factors in a quantitative manner.

Most of these methods have utilized the technic of cataphoresis Thus, Svedberg and Tiselius[1] photographed the migrating boundary between egg albumin and a buffer solution by the aid of the fluorescence produced by protein solutions in ultra-violet light. Loeb[2] coated particles of collodion with various proteins and observed with the aid of an ultra-microscope the direction and rate of migration in an electric field.

Freundlich and Abramson,[3] and Abramson[4] adsorbed protein on the surface of quartz particles and studied the influence of pH on the rate and direction of migration of these coated particles. They found that the quartz particles coated with protein behaved as pure protein particles.

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[1] Svedberg, Th., and Tiselius, A., *J. Am. Chem. Soc.*, 1926, xlviii, 2272.

[2] Loeb, J., *J. Gen. Physiol.*, 1923, v, 395.

[3] Freundlich, H., and Abramson, H. A., *Z. physik. Chem.*, 1927, cxxviii, 25.

[4] Abramson, H. A., *J. Am. Chem. Soc.*, 1928, l, 390.

Briggs[5] has recently demonstrated that the streaming potential can be used as a rapid and extremely accurate method for determining the sign and magnitude of the ζ-potential. This method involves forcing liquid through the pores of a diaphragm and measuring the potential set up across the diaphragm. It seemed probable that a quartz diaphragm coated with protein would act as a protein diaphragm and allow for a rapid and accurate determination of the ζ-potential on the protein. Experiments to test this hypothesis were successful. It was found that the curves of Abramson[4] for quartz-egg albumin could be duplicated, and that the experimental error of the determination was apparently appreciably less when the streaming potential method was used, than when cataphoretic technic was employed. The streaming potential method (as described by Briggs[5]) is far simpler to operate and is less subject to error, inasmuch as it does not involve the determination of the limits of the boundary between the protein sol and the buffer, as in Svedberg's method, and is independent of convection currents and surface streaming which are troublesome factors in ultra-microscopic measurements of cataphoretic mobility. In addition to being more accurate, the streaming potential method is far more rapid. The same quartz-protein membrane may be used to follow the charge in the electrokinetic potential over a given pH range by simply altering the pH of the solution being streamed through the membrane. No streaming potential is set up at the isoelectric point. Accordingly, this method should prove exceedingly useful for determining the isoelectric point of proteins. With care, the method is capable of determining the isoelectric point with as high an accuracy as can be obtained in an electrometric pH measurement.

4088

Glass Surfaces versus Paraffin Surfaces in Blood-Clotting Phenomena—A Hypothesis.

ROSS AIKEN GORTNER AND DAVID R. BRIGGS.

From the Division of Agricultural Biochemistry, University of Minnesota.

It is well known that when blood is drawn through a bare glass cannula or into a glass container, clotting occurs within a very short period of time. On the other hand, if the glass cannula and the container be coated with paraffin so that the blood does not come in contact with the bare glass, clotting may be delayed for hours, or completely inhibited.

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[5] Briggs, D. R., *J. Phys. Chem.*, 1928, xxxii, 641.

Briggs has shown in the preceding communication that a quartz diaphragm may be coated with protein so as to acquire the properties of a pure protein diaphragm. Undoubtedly this is due to the phenomenon of adsorption, possibly in accordance with the Gibbs principle that substances which decrease surface or interfacial tension tend to be adsorbed.

It occurred to us that possibly blood-clotting was dependent upon the adsorption of some constituent from the serum onto a surface, thereby increasing the effective concentration of this constituent and initiating the clotting phenomenon.

Streaming potential measurements showed that a bare glass capillary had a negative ζ-potential of approximately 30 millivolts,* whereas the same capillary coated with a thin layer of paraffin had essentially a zero ζ-potential against water. The high ζ-potential would favor electrostatic adsorption of positively charged colloids at the interface of glass-blood serum, and there would be no such tendency for a paraffin-blood serum interface. We accordingly postulate that the initial step in blood-clotting involves a surface concentration of some positively charged constituent, the concentration being brought about by selective adsorption.

4089

Experimental Production of Auricular Fibrillation by Several Stimuli Applied to the Auricle.

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From the Department of Pharmacology, University of Minnesota.

Auricular fibrillation has hitherto been produced experimentally only by faradization of the auricle, and under these conditions the period of fibrillation rarely outlasts the period of stimulation. Moreover, though it is usually possible to cause spontaneous auricular fibrillation in the dog to cease abruptly after the injection of quinidine it is, as Alfred Cohn has reported,[1] only rarely possible to stop the fibrillation during faradization of the auricle. This practically prevents a satisfactory experimental study of the drugs that might be used to influence auricular fibrillation.

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* The actual streaming potential which was measured between the 2 ends of the glass capillary was in excess of 4.5 volts at 30 cm. Hg hydrostatic pressure. With the same tube coated on the inside with a thin layer of paraffin, the streaming potential was essentially zero.

In this investigation we have produced auricular fibrillation in dogs by throwing into the auricle a cycle of 3 independent make and break induction shocks, about one-eighth of a second apart, each shock being applied to a different part of the auricle. The fibrillary contractions were easily visible in the wall of the auricle and in the electrocardiogram, and were accompanied by the usual absolute arrhythmia in the carotid pulse tracing recorded with a membrane manometer.

In these experiments we used the make and break secondary shocks from 3 independent Harvard induction coils, the secondary circuits of which led to a cylindrical electrode containing 4 insulated wires whose bare ends were about 2 mm. apart. One of these wires was connected with all 3 induction coils in order to complete the 3 circuits. The poles of the 3 primary circuits were connected with a dry cell and then with the base of a Harvard kymograph, the drum of which was covered with a piece of glazed paper bearing 3 perforations made in an oblique descending line, each perforation about 5 mm. in front and above the next one. As the drum was rotated rapidly, a contact was made whenever one of these perforations moved past a spring brass wire set upon a ring stand (from which it was insulated) and this brass wire passed to the second electrode in the primary circuit of one of the induction coils. As the drum rotated once in 6 seconds, this gave a cycle of 3 independent stimuli to different parts of the auricle with an interval of about one-eighth of a second between them. This is about equal to the A-V conduction time.

A single cycle of these stimuli sufficed to set up a "circus movement" in the auricle and in every experiment but one resulted in the development of fibrillation. In almost every experiment we were able to obtain periods of fibrillation which greatly outlasted the periods of stimulation. The fibrillation sometimes lasted from one-half to 2 hours, and we were able to obtain lasting fibrillation by this method in a number of dogs when fibrillation produced by faradization ceased within a few seconds after cessation of the stimulation.

Fibrillation produced in this way was cut short almost immediately by the injection of a few cubic centimeters of 1% quinidine sulphate solution. It is also significant that the only experiment in which we have failed to produce fibrillation was in a dog which showed spontaneous fibrillation when the chest wall was removed, and in which the fibrillation had been stopped by a large dose of quinidine before stimulation was attempted.

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[1] Cohn, A. E., and Levy, R., PROC. SOC. EXP. BIOL. AND MED., 1921, xviii, 283; *J. Am. Med. Assn.*, 1921, lxxvi, 1605.

In our experiments, whenever the stimuli have been applied to rapidly beating hearts, either during stimulation of the accelerators, after atropinization, or after small doses of epinephrine, the resulting fibrillation has never lasted more than a few seconds, whereas we have usually obtained fibrillation lasting from half a minute to 2 hours when the stimuli have been applied to hearts whose vagi were being stimulated either electrically, with pilocarpine or with large doses of epinephrine.

Further studies upon the influence of these factors, as well as upon variations in acid-base equilibria, effects of ions, etc., are in progress.

4090

Effects of Epinephrine Injections upon Deep and Superficial Blood Vessels of Frog's Tongue.

ARTHUR D. HIRSCHFELDER AND CHARLES BLUMENFELD.

From the Department of Pharmacology, University of Minnesota.

Investigations by Cannon and his collaborators[1, 2, 3, 4] have shown that while intravenous injections of epinephrine cause the whole limb to decrease in volume, an increase in volume may be recorded if the skin of the limb has been removed. In other words, epinephrine causes vasoconstriction in the vessels of the skin but not in those of the muscle. We have observed a similar phenomenon in the arterioles of the frog's tongue. If the frog's tongue is observed under the microscope, the superficial capillaries supplying the mucous membrane can be seen as loops closely resembling the familiar capillary loops in the human skin, while the deeper vessels supplying the muscles of the tongue run a much less tortuous course. After the injection of 1.5 cc. of 1:100,000 epinephrine solution into the dorsal or ventral lymph sac, most of the super-

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[1] Cannon, W. B., and Lyman, H., *Am. J. Physiol.*, 1913, xxxi, 376.

[2] Gruber, C. M., *Am. J. Physiol.*, 1918, xlv, 302.

[3] Hartman, F. A., and Kilborn, L. G., *Am. J. Physiol.*, 1918, xlv, 111.

[4] Hartman, F. A., Kilborn, L. G., and Fraser, L., *Am. J. Physiol.*, 1918, xlvi, 168.

ficial capillaries become perfectly bloodless, while in others, the flow of blood corpuscles is greatly retarded. No such contraction or retardation can be noted, however, in the deeper capillaries and arterioles supplying the muscles of the tongue.

These observations show that the same contrast between the effects of epinephrine on the superficial vessels and in the deeper vessels takes place in the frog as has been observed in mammals.

4091

Inhibiting Effects of Lipoids upon Actions of Antiseptics.

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From the Department of Pharmacology, University of Minnesota.

Although many experiments have been performed which have shown that the antiseptics have a weaker action in blood serum and tissue juice than in water salt solution or bouillon, this diminution of action has always been ascribed to the presence of the proteins. However, since these fluids also contain lipoids, and since, as has been shown by Cruikshank,[1] Loewe[2] and others, the lipoids may play a decided rôle in altering the distribution coefficient of the antiseptic dyes, we have studied the effects of the mere presence of lipoids upon the action of various antiseptics. In the experiments which we have performed, we have found that when cultures of *Staphylococcus aureus* and *Bacillus coli* are exposed to the action of various antiseptics (acriflavine, pyridium, phenol, bichloride of mercury) in suspensions of 0.5% lecithin or kephalin, or of .05% cholesterol, the antiseptic activity was greatly weakened; and this decrease of effectiveness is of about a degree similar to that which is brought about by the presence of an equal concentration of protein, though usually somewhat less marked. Since blood plasma contains .25% lecithin and .18% cholesterol, suspensions which we have used are quite comparable to blood plasma.

The table below gives the greatest dilution in Clark's buffer solutions ($Na_2HPO_4+KH_2PO_4$ at pH 7.4) of the antiseptics which inhibited the growth of transplants to agar after the bacteria have been exposed to the action of the antiseptic for 3 hours. The experiments with pyridium were done in Locke's solution as the antiseptic is precipitated by the phosphate buffer at pH 7.4.

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[1] Cruickshank, J., *J. Path. and Bact.*, 1920, xxiii, 230.

[2] Loewe, S., *Biochem. Z.*, 1922, cxxvii, 231.

TABLE I.

Staphylococcus aureus.

	Neutral Acriflavine	Pyridium	$HgCl_2$
Control	1:8,000	1:8,000	1:750,000
0.5% Lecithin	1:4,000	1:2,000 growth+	1:16,000
0.5% Cephalin	1:4,000	1:2,000 growth+	1:4,000
0.05% Cholesterol	1:4,000		

Bacillus coli.

	Neutral Acriflavine	Pyridium
Control	1:8,000	1:8,000
0.5% Lecithin	1:1,000	1:2,000
0.5% Cephalin	1:1,000	growth in 1:2,000
0.05% Cholesterol	1:8,000	

Longer exposure to these antiseptics gave commensurate results except in the case of acriflavine and cholesterol, in which the control showed no growth in 1:54,000 after 12 hours and 1:500,000 after 24 hours, while in the presence of .05% cholesterol, inhibition occurred in 1:16,000 after 12 hours, and in 1:100,000 after 24 hours.

These results were obtained even in the absence of any visible flocculation of the lipoid suspension.

We have also observed with the ultramicroscope the effect of antiseptic on lipoid emulsions. The quinine series give blue or greenish Tyndall cones, though no particles can be seen. Lecithin emulsion shows large slowly moving particles. With addition of quinine, for instance, the particles may be seen to form large clumps, and clots are formed, while the blue Tyndall cone becomes weaker, and if sufficient lecithin is added, disappears. Similar results are obtained with the yellow cone of acriflavine.

Mercury is the only heavy metal which does not precipitate a lecithin emulsion, and no change in the ultramicroscopic picture is seen when $HgCl_2$ is added. However, the striking decrease in the effective antiseptic concentration shows that the bichloride is combined in some way. $AgNO_3$ rapidly produces clots.

Cholesterol shows an immediate and striking effect on the Tyndall cones of quinine, ethyl hydrocuprein, eucupin and vuzin, of fluorescein and eosin, and of acriflavine and rivanol. The cholesterol particles are small, bright and rapidly moving. The above antiseptics combine quickly with these particles, losing their fluorescent property. $HgCl_2$ and $AgNO_3$ cause the rapid formation of clots.

It may be noted that in our experiments with the basic antiseptics, acriflavine and pyridium, we found the Gram positive *Staphylococcus aureus* and the Gram negative *Bacillus coli* equally sensitive to the dyes. This harmonizes with the results of Hirschfelder, Jensen and Swanson,[3] and of Skinner and Burke,[4] and is in striking contrast with the oft repeated claims of Churchman,[5] that Gram positive microorganisms are more sensitive to basic dyes and the Gram negative ones more sensitive to the acid dyes.

Our experiments indicate that the effect of the lipoids as well as of the proteins of blood plasma, serum and tissues, must be taken into account, as well as that of the proteins, in the study of the action of antiseptics.

We take pleasure in acknowledging our indebtedness to Dr. R. A. Gortner for the privilege of using the Szigmondy slit ultramicroscope and for his aid in this part of the work.

4092

Iodine Content of Milk Powder.

DON R. MATHIESON. (Introduced by J. F. McClendon.)

From the Laboratory of Physiological Chemistry, University of Minnesota.

A sample of powdered whole milk from Indiana (goitrous region) was found to contain 166 parts of iodine per billion; and a sample of lactic acid milk from the same source was found to contain 44 parts per billion.

These values may be compared with 62 parts per billion (dry basis) for milk from Berne, Switzerland (goitrous region) and 400 parts per billion for milk from the California Coast where the feed was bathed by sea spray (non-goitrous region).

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[3] Hirschfelder, A. D., Jensen, H. H., and Swanson, W. W., PROC. SOC. EXP. BIOL. AND MED., 1923, xx, 402.

[4] Burke, V., and Skinner, C. E., *J. Exp. Med.*, 1924, xxxix, 613.

[5] Churchman, J., *J. Exp. Med.*, 1912, xvi, 221; 1913, xvii, 373; 1921, xxxiii, 569; *J. Am. Med. Assn.*, 1918, lxx, 1047; 1921, lxxvii, 24; 1922, lxxix, 1657; PROC. SOC. EXP. BIOL. AND MED., 1923, xx, 402.

4093

A Simple Method for Determination of Threshold Value of Vibration Sense.

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Symns[1] has described the first method for the quantitative determination of vibration sense. In his fork 2 pieces of steel are attached to the prongs so that when the fork is vibrating strongly a small window is seen between them and this window disappears at a certain amplitude of vibration. On the disappearance of the window the fork is applied to a bony point of the patient and a stop watch started. When the patient no longer feels the vibration the watch is stopped. It is assumed then that vibration sense is relatively less acute, the shorter the time interval during which it is perceived. This work has been continued by Wood[2] and Ahrens.[3]

In observing a fork vibrating under a microscope it is evident that when the amplitude is small, the vibration recedes very slowly, so that even with the eye observing the fork directly and aided with an eyepiece micrometer, it is difficult to determine within several sec-

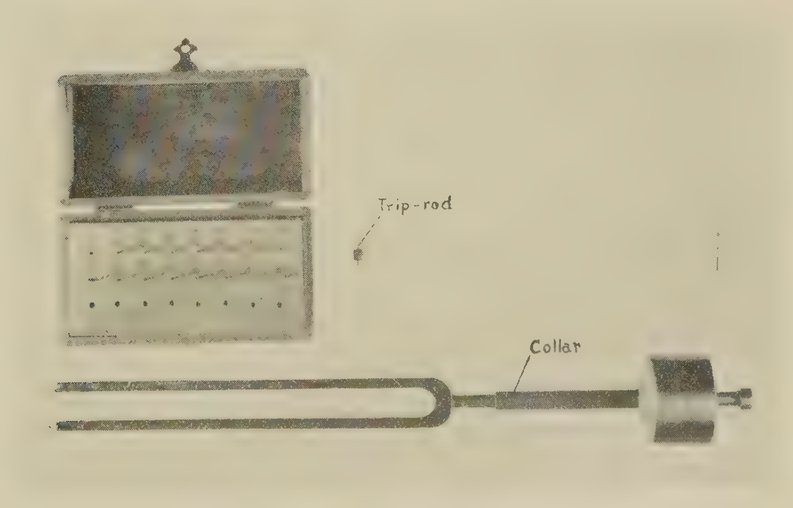

FIG. 1.
Materials necessary in this method of testing vibration sense.

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[1] Symns, J. Ll. M., *Brit. Med. J.*, 1912, i, 539; *Guy's Hosp Rep.*, 1912, lxvi, 120; *Quart. J. Med.*, 1917, xi, 33.

[2] Wood, E. J., *Am. J. Med. Sc.*, 1922, clxiii, 19.

[3] Ahrens, R. S., *Arch. Neur. Psych.*, 1925, xiv, 793.

onds of time when the fork is vibrating exactly at a given amplitude. Then, too, from the physiologic standpoint it has often been stated that in testing sensation one should approach the threshold value from below rather than from above as is done with Symns' fork. Further, there is no easy method of keeping the pressure of the fork constant on the bony point of the patient.

With these difficulties of the former method in mind, the technique here described was developed.

The materials necessary are shown in Fig. 1. The tuning fork is 10½ inches in length and has a rate of 128 vibrations per second. The base of the fork has been weighted so that altogether it weighs 501 gm. Around the shank of the base is a metal collar which slides freely up and down. Thus the fork can be supported in a vertical position by holding the collar so that it will not tip over and it will then rest with approximately 500 gm. pressure on the portion of the patient to be tested. The contact phlange of the bottom of the fork which rests against the patient is 1.0 cm. in diameter. The small box shown in Fig. 1 contains 15 rods made from piano wire which is 1.50 mm. in diameter. These rods range in length from 13.90 mm. to 19.00 mm. ± 0.01 mm. The rods can be pushed through a small cylindrical piece of rubber which is attached to the end of a silk thread about 20 cm. in length. On the other end of this silk thread is a small metal rod for convenience in handling. The piano wire rods are pushed through the rubber on the tip of the thread and are placed between the prongs of the fork thus spreading the prongs at will from 13.90 mm. to 19.00 mm. Then by quick traction on the thread the rod is jerked from between the prongs of the fork and the initial vibration of the fork will correspond closely to the amount of spread produced by the piano wire rod. Kielhauser[4] states that rods have been used by Müller, Pouillet and Pfaundler to start forks vibrating.

The accuracy of the method has been tested out as follows:

The fork is clamped in a horizontal position by its shank in a vise. Its tip is observed through an erecting microscope fitted with a Spencer eyepiece micrometer. The tip of the fork is illuminated by an arc light and a bull's eye condenser. A tiny scratch at the tip of the fork is located by the very bright light which it reflects into the microscope. When the fork is caused to vibrate, this tiny scratch becomes a line which is easily measured for length by means of the eyepiece micrometer. The length of this line, of course, corresponds to the apparent amplitude of vibration of the fork and the actual amplitude is computed from the fact that, with the magnification used, each distance between any 2 lines in the eyepiece micrometer corresponds to 0.14 mm. in actuality. This distance between any 2 lines of the eyepiece micrometer is of such size that it is easy to estimate tenths of the distance and tenths, therefore, correspond to 0.014 mm.

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[4] Kielhauser, E. A., *Verlag von B. G. Teubner*, Leipzig, 1907.

Determinations were made of the initial vibration produced by each one of the 15 rods. Twenty-five readings were taken from each rod. Their average values are plotted in Fig. 2. Opposite each average observation in this figure is placed the numerical expression for the average and this is followed in parenthesis by the extreme range of the observation. Since the distance between the prongs of the fork at rest is 13.75 mm. one would expect the 14.00 mm. trip rod to produce a vibration of 0.25 mm. and the 19.00 mm. rod to produce an initial amplitude of 5.25 mm. It is seen in Fig. 2 that the 14.00 mm. rod produces an average initial amplitude of vibration of 0.238 mm. while the 19.00 mm. rod produces one of

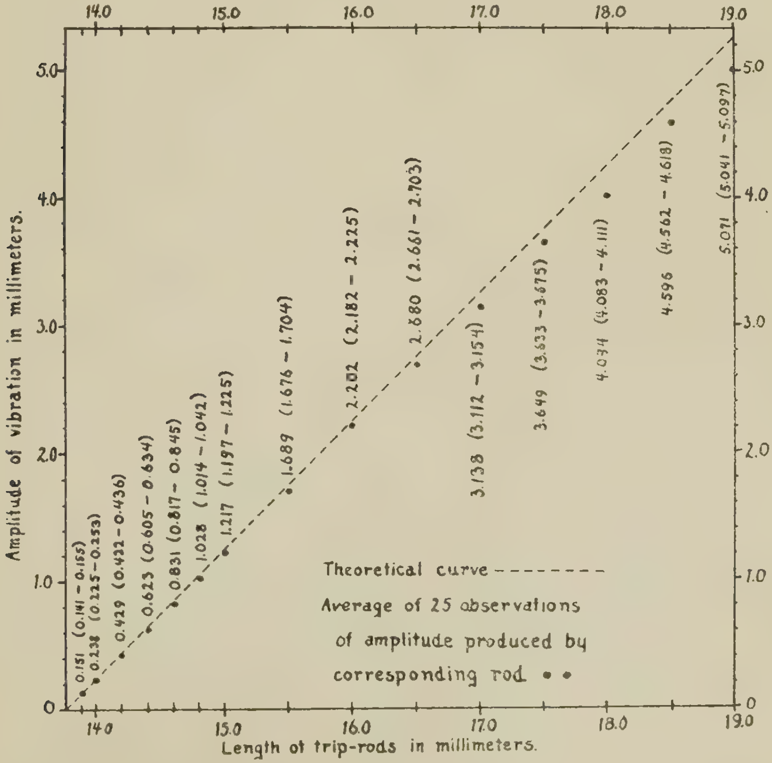

FIG. 2.

Theoretical curve and average amplitudes produced by the various rods.

5.071 mm. The theoretical curve which one would expect these readings to follow is plotted in the dashed line of Fig. 2, while the average of the actual observations is shown by dots. It is seen that as the longer rods are used, the amplitude of the initial vibration becomes progressively less than one would expect from the theoretical curve. No doubt this discrepancy is due to the increased friction, air resistance and the like which becomes more and more marked as the length of the rods is increased. The greatest range of variability of the readings of initial amplitude is found to be with the 18.50 mm. and the 19.00 mm. rods, which show a range of 4.562 mm. to 4.618 mm. and 5.041 mm. to 5.097 mm. respectively. The extreme range of error, therefore, is only 0.056 mm. In making these readings it has been found that if the trip-rod is pulled from the fork in a direction more than 5° or 6° towards one or the other prong of the fork, the initial vibration is larger than when the rod is pulled more in the axis of the fork. This seems to be the only technical point of any difficulty which one must remember in using this fork.

In observing a tuning fork it becomes evident that the more forcibly the fork is started, the more rapidly it runs down at first, whereas it will continue to vibrate at a relatively small amplitude for a rather long period of time. In order to obtain some data on this point, a kymograph drum was rotated at a constant speed. On this kymograph drum seconds were marked off with an electric time-marker activated by a metronome. Another signal magnet was placed on the drum in a different electric circuit so that one could make contacts at recorded intervals of time. The tuning fork was observed under the microscope as already described. The fork was then activated by the longest (19.00 mm.) rod. As the fork was started a contact was made in the circuit and as the amplitude receded past the first 8 marks in the micrometer a second contact was made. As it ran past the 16th mark in the micrometer another contact was made and then one for each successive alternate mark. In this way it was possible to determine fairly accurately the time intervals which were used up by the fork in receding from its maximum amplitude through successively smaller amplitudes of vibration. The curve of the recession is shown in Fig. 3. On the inner side of each vertical margin of Fig. 3 are indicated the various trip-rods which are identified by their respective lengths, and are arranged in the position of the average amplitude which they produce in terms of micrometer graduations. It is seen that, in receding from the initial vibration amplitude produced by the 19.00 mm. rod to the 18.50 mm. rod, about 0.5 seconds are used up. A similarly small interval of time is required for recession to the 18.00 mm.

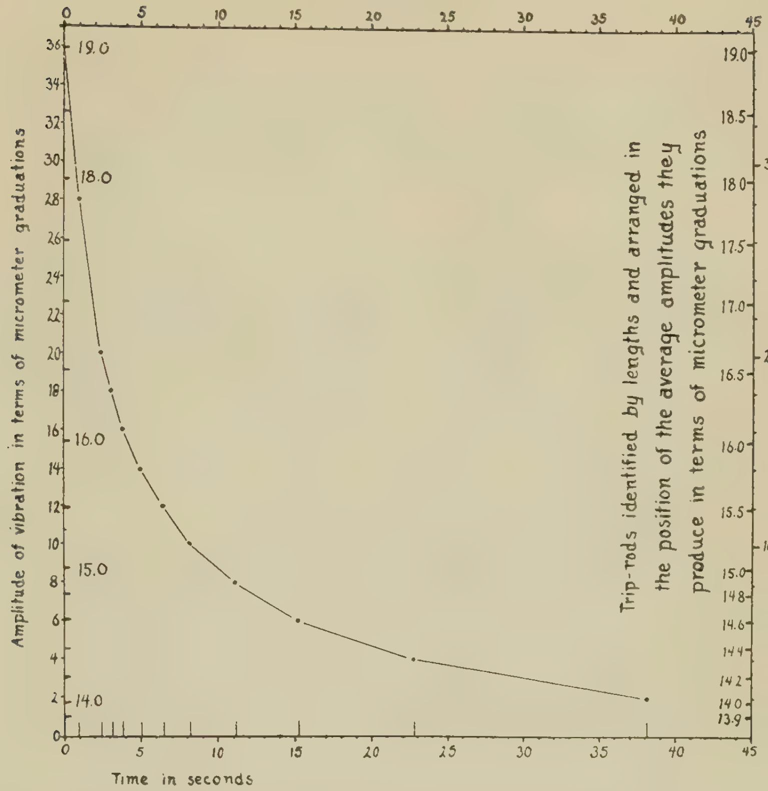

FIG. 3.

Curve of recession of the amplitude of vibration of the fork. The fork did not come to rest until approximately 145 seconds in all had elapsed.

rod and again to the 17.50 mm. rod. From the 17.00 mm. rod on down the time intervals become longer and longer. It is evident from this plotting that a patient who is being tested will have such a short interval in which to recognize the vibration initiated by the longer rods that it is probably impractical clinically to use rods of greater length than 17.00 mm. or 17.50 mm. with this particular fork.

Conceivably, temperature might change the amplitudes set up by the trip-rods. This was tested by making 5 measurements at room temperature with one of the rods, and then by 5 measurements with the fork heated by a Bunsen flame to a temperature almost unbearable to the naked hand. The average difference in the 2 sets of readings was less than 0.014 mm. which, in turn is less than the range of variability of the readings already presented.

Clinical work with the method described in the foregoing is in progress and will be reported later.

4094

Blood Pressure and Blood Protein Determinations in the Frog.

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In a previous note,[1] the authors called attention to the low protein content of frog's blood. The low colloidal pressure of the blood is an important factor in determining the production of urine. The blood pressure of the frog is not nearly as high as in mammals, but if filtration is the basis of glomerular activity, there should be enough pressure to overcome the osmotic pressure of the colloids of the frog's blood.

It seemed desirable, therefore, to make some actual blood pressure determinations and determinations of the protein content of the blood on the same animal.

In order to make blood pressure determinations on the intact animal, the following apparatus was devised. A modified apparatus such as is used for determining arterial blood pressure in man was used. Small rubber cuffs were constructed from small rubber balloons, varying in size from one-half to one inch wide, and 3 to 5 inches long. A rubber tube was cemented into the open end of the balloon and by means of it the balloon was connected to a mercury manometer, an outlet valve, a Woolf bottle to act as a buffer, and a rubber atomizer bulb. The frog was placed in a suitably sized box with its right leg protruding through a small opening. The rubber cuff was then wrapped around the thigh or leg, the web of the foot placed under the low power of the microscope and as large an arteriole as could be found was brought into focus. A pulsating stream could be observed. The pressure in the cuff recorded by the mercury manometer was raised until pulsations in the arteriole could no longer be seen. The air was then gradually let out of the system and when pulsations first were observed, the mercury manometer was read for systolic pressure. As the pressure continued to fall slowly, it was noticed that between systolic peaks of pressure, the blood stream slowed to complete stoppage and sometimes to a reverse flow. When this reverse flow disappeared and the stoppage between systoles began to disappear, the diastolic pressure was taken. The readings obtained in this manner have been checked up with a mercury manometer attached directly to an artery in the abdominal cavity and with a Hurthle manometer attached in the same manner, and the readings were found to be within the limit of error.

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[1] Scott, F. H., and Bieter, R. N., PROC. SOC. EXP. BIOL. AND MED., 1922, xx, 120.

Blood pressure readings have been taken in a series of small frogs *(Rana pipiens)* and also in a series of large frogs *(Rana catasbiana)*, after which these animals were bled for plasma protein determinations.

The determinations of the protein content were made as follows: After the blood pressure determinations had been made, 5 mg. of heparin were injected subcutaneously into the large frogs and 1 mg. into the small ones. After waiting about half an hour, the animals were etherized, a cannula inserted into the coeliac axis in the large frogs and the frogs bled. In the case of the large frogs, the blood was taken in 2 parts; the first sample (2-5 cc.) came rapidly; the second sample of about the same amount came slowly, sometimes 20 to 30 minutes. In the case of the small frogs, the tip of the ventricle was snipped off and allowed to bleed into a small tube. The tubes were centrifuged and a definite volume of clear plasma removed with a pipette. This was placed in a weighed centrifuge tube and 10% trichloracetic acid added in excess. After standing, the tube was centrifuged, the supernatant fluid removed, more trichloracetic acid added, and recentrifuged. The supernatant fluid was removed and the same process repeated with 70% absolute alcohol. The tubes were then placed in an oven at 102° and dried to a constant weight.

The blood pressure of the frog was found to be quite variable at first. As a result of struggling, systolic pressures as high as 7 mm. Hg. have been observed. However, after a while, the pressures became fairly stable, ranging around 25-35 systolic to 18-28 diastolic and giving a pulse pressure of 7-10 mm.

The proteins (trichloracetic acid precipitate) of the plasma ran, ordinarily about 3.7% on the first or normal sample of blood, the variations being from 4.48% to 2.7%. As a result of the hemorrhage, the protein content of the second sample was frequently cut in half. Attention has been called by one of the authors[2] to the fact that the fluid entering the blood of mammals after hemorrhage is practically pure salt solution. The same fact is observed here. Little difference was observed in the blood pressures of the large or small frogs, but the protein content of the small *(R. pipiens)* frog was usually somewhat less than that of the large frog *(R. catasbiana)*. The highest figure given by Krogh[3] for the osmotic pressure of frog's blood is 40 mm. H_2O for 1% protein. White[4] gives practically the same figure. There is thus seen to be plenty of filtration pressure to produce urine in the frog, the systolic pressure being about 3 times the osmotic pressure of the colloids.

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[2] Scott, F. H., *J. Physiol.*, 1916, l, 157.

[3] Krogh, A., *Anatomy and Physiology of Capillaries*, 1922.

4095

Significant Difference in Response of Pernicious Anemia to Fetal Calf and Beef Liver Feeding.

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A marked increase in the number of circulating reticulocytes represents a well-known feature in the response of patients with pernicious anemia to the feeding of beef liver or of the Cohn-Minot liver extract. So constant is this response that the reticulocyte curve is being used in the testing of the potency of extracts. An equally constant but usually less pronounced feature is the pouring out of an increased number of erythroblasts into the circulation, which phenomena precedes the reticulocyte increase by a few days. Biologically both these phenomena are reliable indications of a certain lag in the complete cell maturation.

TABLE I.
Subject: Mrs. Q. U. Hosp. No. 43942. Diagnosis: Pernicious Anemia.

Day of observation	Erythrocytes millions per cu. mm.	Reticulocytes in % of erythrocytes	Hemoglobin	Remarks.
1	1.08	1.5	31	On liver extract, potency unknown.
3	1.33	1.8	33	
5	1.36	3.4	33	
7	1.24	2.4	33	
9	1.19	1.8	32	
11	1.20	1.3	35	From 10th day on powdered fetal liver.
13	1.34	1.6	39	
15	1.38	1.8	41	
17	1.40	1.6	40	
19	1.70	.6	42	
21	1.85	.4	43	
23	1.90	.8	47	
25	2.10	.6	51	

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[4] White, H. L., *Am. J. Physiol.*, 1924, lxviii, 523.

In this paper we present an instance of complete maturation of the erythrocytes during the whole of an induced rapid remission in a typical severe case of pernicious anemia (woman, age 41, Hosp. No. 43942). The remission was produced by the feeding of powdered fetal calf's liver, in amounts corresponding to 300 g. of fresh liver a day. This remission followed immediately upon an unsuccessful trial of corresponding doses of a beef liver extract, the potency of which had not been previously ascertained. As seen from Table I, there was at first during the liver extract period some definite response with a slight increase in the number of erythrocytes and an increase of the reticulocytes up to 3.9%. Both these changes were, however, transitory. As an unfavorable sign megaloblasts appeared in the circulation in increased number.

With the onset of the fetal liver feeding the erythrocytes started again to show a steady increase in number, and the megaloblasts disappeared promptly. The normoblasts which had been present in small number during the whole period of observation did not increase, and the reticulocytes remained below 2%, soon falling as low as about half of 1%. On beef liver extract the corresponding reticulocyte counts would have gone as high as 15% or more.

4096

Statistical Significance of Erythrocyte Counts During Responses to Liver Extract in Normal Individual.

HILDING BERGLUND, CHARLES H. WATKINS AND RICHARD JOHNSON.

From the Medical Service of the University Hospital, and the Department of Anatomy, University of Minnesota, Minneapolis.

Marked increases in the number of circulating erythrocytes have recently been reported following the administration of the Cohn-Minot liver extract to normal individuals.[1] The outstanding features of the curves obtained were 2: rapid and considerable increases as well as marked irregularities in the number of erythrocytes leading to deep and abrupt depressions alternating with peaks. The curves were constructed from daily blood counts.

It seems desirable to supplement these observations by more frequent determinations of the number of erythrocytes, as well as by an inquiry into the statistical significance of the erythrocyte counts. One of the persons (H. B-d) who had previously in 2 separate experiments responded to the liver extract both with peaks up to 7,870,000 and 7,700,000 erythrocytes respectively and with deep depressions was chosen for the experiment. The erythrocyte counts of this individual have been consistent over a number of years. As early as 1906 the counts gave values of 5,500,000 (mean of 5 or 6 determinations) and in the 2 recent experiments the curves started at a level of 5,950,000 and 5,400,000 respectively.

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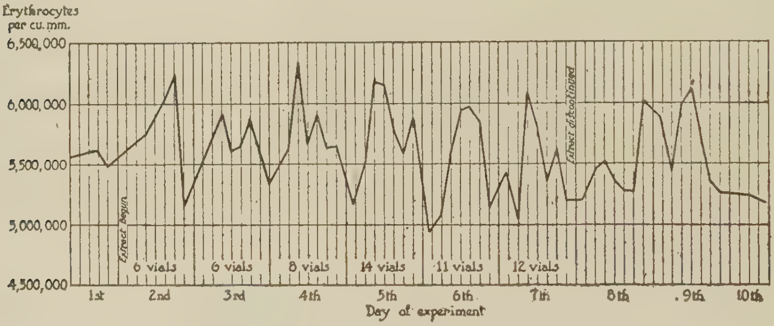
[1] Watkins, C. H., Johnson, R., and Berglund, H., PROC. SOC. EXP. BIOL. AND MED., 1928, xxv, 720.

In order to determine the significance of the variations in the erythrocyte counts in the normal individual, observations were made at 3 hour intervals during the day before liver extract was started. Following this, the Cohn-Minot liver extract (Lilly 343; lots 29157-815244-815245) was given for 6 days in the dosages shown in Graph 1. On the 1st day counts were made at 3 hour intervals from 9:00 a. m. to 9:00 p. m. On the 2nd and 3rd days counts were made at 3 hour intervals from 6:00 a. m. to 12:00 midnight, and on the remaining 5 days counts at 2:00 a. m. were substituted for those at midnight. Each time erythrocyte counts were made, blood was taken from 3 fingers, using a different pipette for each finger. Three counts were then made from each pipette, making only one count for each filling of the counting chamber, giving a total of 9 counts for each period of the day. In making each count the cells covering 80 small squares were counted. The mean, standard deviation and probable error of the mean were calculated for each series of 9 counts. Comparisons were made of the means for different times of the normal day with the means for all other times of that day, and the significance of the difference tested by the



GRAPH 1.

A graph illustrating the variations of the means of erythrocyte counts, plotted in succession.

Abscissa: Days of experiment. Ordinate: Means of erythrocyte counts.

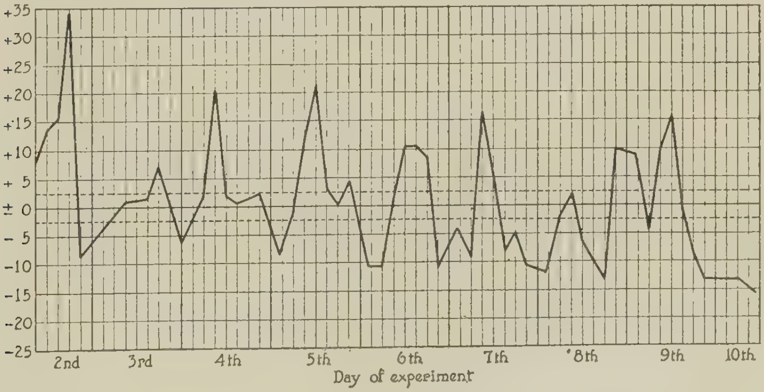
usual formula for the probable error of a difference. The differences of the means for the pre-liver day were found to be statistically insignificant. Therefore all of the data for the pre-liver day were grouped in one series to establish a mean for use as a normal base.

Similar comparisons were made for the first 2 days after liver extract was started. Only seriatim comparisons were made for the remaining 7 days. With a few exceptions, the differences show a high statistical significance. The ratios of the differences to their probable errors range from 0.06 to 21.23. Of the 64 ratios computed, but 16 are less than 2.5 and are of questionable statistical significance.

The preponderance of the large difference ratios indicates that the variation of the blood counts from time to time, under liver extract stimulation, is significantly different from the blood count prior to this stimulation, for there is no evidence of significant variation during the pre-liver day.

The series of means for the normal day and for the days of the administration of liver extract and for 2½ days following the same are plotted in succession in Graph 1.

The ratios of the differences of the means to their probable errors, for blood counts on liver days as compared with the blood counts of the pre-liver day, are shown in Graph 2. The 54 ratios range from 0.26 to 34.44. Of these 16 are less than 2.5. This con-



GRAPH 2.

A graph illustrating the variations of the ratios of the differences of the successive means from the mean to the probable errors of these differences. The conventional zone of questionable statistical significance is indicated between the dotted lines.

Abscissa: Days of experiment. Ordinate: Ratios of the differences of successive means from the initial mean, to the probable errors of these differences.

ventional zone of insignificance is indicated on the graph by the dotted line on each side of the base line. Here again the preponderance of significant differences seems to indicate that there is a marked effect on the erythrocyte count, following the administration of liver extract.

The statistical significance of the observations having been established and properly defined, Graph 1 presents itself for biological consideration. The character of the response previously established for normal individuals to liver extract is decidedly more complicated than was suspected from our previous daily observations. There is produced through the liver extract a series of reactions, which reoccur with unmistakable periodicity. This periodicity seems to be approximately of a 24 hour type. A strong factor is present tending towards increasing the concentration of circulating erythrocytes. This factor is evidently checked by another force aiming to preserve a lower erythrocyte level. With the tendency towards a high erythrocyte level remaining about constant throughout the experiment, the force to establish a lower level is gaining as the experiment progresses, leaving the subject with a final level lower than the initial one. In this connection attention should be called to the fact that the subject of the experiment during 2 previous experiments responded with blood counts one a half million higher than in this experiment. That this difference is not due to a difference in the potency of the extracts used is indicated by the clear independence of the height of the peaks in this experiment of the amount of extract taken.* An increase in strength of the lowering factor during the different experiments as well as during the course of this experiment is suggestive. The temporary persistence of the effect after the extract had been discontinued is noticeable.

It is possible that through the exaggerated conditions of the experiment an expression of the normal mechanism for the regulation of the erythrocyte level has been brought to light, a mechanism which under normal conditions is perhaps difficult or impossible clearly to observe.

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* This supposition is perhaps not correct. Dr. George Minot just informs me that the lots used were checked up as being about 35% and 50% weaker than standard respectively.

Illinois Branch.

City Club, Chicago, May 25, 1928.

4097

Calcium Excretion by the Alimentary Tract.

E. L. WALSH AND A. C. IVY.

From the Department of Physiology, Northwestern University Medical School.

It is generally accepted that calcium is absorbed in the upper and excreted in the lower intestine. Since, so far as we have been able to ascertain, none of the experiments used by the various investigators has involved the use of pouches or fistulas of the various portions of the intestine in unanesthetized animals, we decided to study calcium excretion by using such a method. We believe this method has the definite advantage that every possible factor can be quite accurately controlled.

Stewart and Percival,[1] in acute experiments on cats, showed by washing of the colon that apparently there was a constant excretion of calcium by the colon, averaging about 0.8 mg., for the 3 hours.

Pouches (Thiry-Vella) of the upper jejunum and the lower ileum about 18 inches long were made; and pouches of the entire colon were made. Only dogs were used. These pouches were washed out at various intervals with distilled water, 0.1% HCl and 0.1% $NaHCO_3$, the amount of calcium in the washings being determined by the permanganate method.

It was found that daily washings with distilled water of the loop, or pouch, of the upper jejunum, yielded from 0.32 to 1.2 mg. of calcium; that daily washings of the pouch of the lower ileum yielded from 2.0 to 8.5 mg.; and that daily washings of the entire colon yielded from 1.8 to 15.0 mg. of calcium. Daily washings with the weak acid and alkaline solutions did not increase the yield. Washing out the lower ileum or colon at one hour intervals in succession for 6 or 8 hours markedly increased the yield, the yield of the lower ileum being from 24.0 to 30.0 mg., and of the colon from

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[1] Stewart, C. P., and Percival, G. H., *Biochem. J.*, 1927, xxi, 301.

17.6 to 55.4 mg., for 8 hours. Experiments are under way to determine the effect of bile, feces and mechanical distension on calcium elimination by the intestine.

It is evident from our experiments that calcium is eliminated to a much greater extent by the lower intestinal mucosa than the upper. However, it must be pointed out that the concentration of calcium in the gastric juice is from 5.0 to 6.5 mg. per 100 cc.[2] of pancreatic juice (our own determination) is from 5.0 to 9.0 mg. per 100 mg., and of gall-bladder bile from 6.0 to 17.0 mg. per 100 cc. It is also evident from our experiments that increased activity of the lower ileum and colon caused by hourly washings markedly increases the output of calcium.

4098

Emptying of Human Gall Bladder After Saline Cathartics.

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In a recent number of the PROCEEDINGS[1] it was shown that magnesium sulphate, when injected directly into the duodenum, produced relatively as great an expulsion of bile from the gall bladder as usually resulted from the first phase of contraction following a meal of egg-yolk. Secondly, the striking change in shape of the cholecystograms made it certain that not merely emptying but also contraction of the gall bladder was induced by the injection of this salt.

Since then, a large number of other salts have been tried, employing the same quantitative method of measuring the response that has been used in our other investigations, namely, computation of successive gall bladder volumes and the plotting of a contraction curve. Up to the present time, this work has revealed the existence of 2 other salts which in strong solutions are as effective as magnesium sulphate, viz., magnesium chloride and sodium sulphate. Furthermore, each of the 2 sulphates when diluted and given by mouth, induce nearly as pronounced an emptying as when given by

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[1] Boyden, E. A., and Saunders, A. M., PROC. SOC. EXP. BIOL. AND MED., 1928, xxv, 458.

[2] Austin, W. C., and Matthew, S. A., *Am. J. Phys.*, 1927, lxxxi, 552.

Rehfuss tube. But magnesium sulphate, when given to cats, either by mouth or by duodenal tube, does not induce emptying of the gall bladder. Similar negative findings in dogs have been recorded by Gantt and Volborth.[2] One of the alternative explanations they suggest is therefore probably correct—that there is a species difference in the reaction of the gall bladder. Yet in both animals and man, magnesium sulphate induces active peristalsis of the intestine. This confirms our previous observations (made upon animals in which the common duct had been severed from the intestine) that peristalsis of the duodenum is not a significant factor in the evacuation of the gall bladder.[3]

Further evidence in this direction is supplied by our experience with such other well known hydragogue cathartics as sodium phosphate and citrate, magnesium citrate and Rochelle salts (tartrates of sodium and potassium) all of which induce peristalsis but none of which cause any pronounced emptying of the gall bladder. Indeed, some of these, as well as hypertonic solutions of sodium chloride and sodium bicarbonate, may close the outlet of the common duct and induce sudden relaxation and filling of the gall bladder. It would seem, therefore, that the action of the 3 effective salts mentioned in the preceding paragraph is best explained on the ground of stimulation of sensory nerve endings by certain specific ions—a hypothesis which is being subjected to further experimentation.

Since much has been written about the effect of gastric secretion upon the action of the gall bladder, especial attention during the course of these experiments has been paid to the contents of the duodenum. The chyme was continuously aspirated and careful records were kept of the changing acidity and alkalinity. Occasionally it was found that a sudden change from an acid to an alkaline medium resulted in immediate relaxation and filling of the gall bladder and abrupt changes in the reverse direction sometimes resulted in a slight emptying of the gall bladder. When various solutions of HCl (in strengths usually found in the stomach) were injected into the duodenum, no such consistent results occurred as had been obtained with the use of foods and effective salts; in some cases the gall bladder dilated, in others its contents diminished, the maximum case being 12 cc. as against the maximum of 45 after egg yolk in the same individual, or of 42 cc. after $MgSO_4$ in the instance previously reported.[1] While these experiments confirm the action of HCl as reported by Ivy and Oldberg,[4] it would seem that hydrochloric acid plays a very insignificant rôle in the emptying of the human gall bladder.

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[2] Gantt, W. H., and v. Volborth, G., *J. Lab. and Clin. Med.*, 1926, ii, 542.

[3] Boyden, E. A., and Birch, C. L., PROC. SOC. EXP. BIOL. AND MED., 1927, xxiv, 827.

Finally, a substance has been found—petrolatum—which separates the action of the gall bladder musculature from that around the outlet of the common duct. In the 2 cases in which this inert mineral oil was injected into the duodenum, an initial relaxation of the gall bladder ensued, followed by increased tonus but no diminution of size. Subsequently when egg yolk was injected, the gall bladder again contracted (as evidenced by the shape of the cholecystograms), but was again unable to discharge its contents—due, presumably to a spastic closure of the outlet of the common duct induced by the presence of petrolatum. But when the patient was given a coarse meal which scoured the oil out, the gall bladder emptied about half of its contents. It would seem, therefore, that by the use of petrolatum we had reproduced the conditions recorded spontaneously in a previous case of hour-glass gall bladder in which the biliary vesicle could be induced to contract but the sphincter remained closed.[5]

4099

Physiological Effects of Temporary Occlusion of the Coronary Vessels.

DON C. SUTTON AND W. W. KING. (Introduced by A. C. Ivy.)

From Northwestern University Medical School.

The following experiments were conceived by Dr. Andrew C. Ivy and myself in an effort to explain the acute effects of sudden occlusion of a coronary artery. The assistance of Dr. Ivy and Mr. Leuth has been essential to the success of these experiments. This work may be divided into 3 phases:

EXPERIMENTS OF SERIES I.

Method: Under ether anesthesia and artificial respiration the chest is opened in the 5th left intercostal space. Through a small incision in the pericardium a ligature is passed around the *ramus descendens* anterior sinister branch of the left coronary artery. Without tying, the 2 ends of the ligature are passed through a flanged glass tube. With a purse string suture the proximal end of the tube is sutured into the pericardium at the same time closing the incision in the pericardium. The proximal end of the tube is sutured to the chest wall and the incision closed with practically no pneumo-thorax remaining. After 3 to 4 hours the dog has completely recovered from the anesthesia and is apparently little harmed by the operation. By fixing the external portion of the glass tube, traction on the ligature compresses the included artery, vein and possibly nerves without displacing the heart. The effects of this procedure are.

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[4] Ivy, A. C., and Oldberg, Eric., *Ibid.*, 1928, xxv, 251.

[5] Boyden, E. A., *Ibid.*, 1927, xxv, 99.

1. Observation—the glass tube and ligature had no evident effect on the heart. Pain is caused by traction. The degree varies in different animals. Almost the moment the traction is released the animal becomes quiet and apparently normal. Pain does not occur when only muscle and pericardium are included in the ligature.

2. Salivation—which is an indication of nausea in the dog, was present 3 times, one dog vomited.

3. Respiration—is violent and irregular as would be expected in pain.

4. Dilatation of the heart was present 4 times to a marked degree. This dilatation is definitely limited by an intact pericardium. The pericardium is tense and when opened, the heart bulges through.

5. Electrocardiograms—During traction show premature contractions, usually of ventricular origin, also of auricular origin. Paroxysmal tachycardia of ventricular origin has been observed. Complete cardiac standstill has been observed varying from 1 to 5 seconds in duration in 3 out of 4 dogs. There is an increase in the amplitude of both the R and T waves. Inversion of the T has been observed in only one dog but it rises quickly from the down stroke of the R as in human electrocardiograms.

EXPERIMENTS OF SERIES II.

A. After section of the vagus nerves, in one dog pain occurred when only the vein was included in the ligature. Great cardiac dilatation occurred.

B. The left stellate ganglion has been removed in 3 dogs. One to 3 weeks later ligatures around the artery failed to produce pain. Salivation was marked in one.

EXPERIMENTS OF SERIES III.

Method: Under Barbital anesthesia and artificial respiration, the chest was laid open exposing the heart. Myocardiograph levers were attached to the right ventricle and right auricle and lead to tambours writing on a smoked drum. Blood pressure was recorded directly from the right carotid artery. The coronary artery is ligated and the ligature runs through a glass tube which is inserted through the chest wall exactly as in the preceding experiment. In this experiment direct observation of the heart is possible, also direct record is made of the auricular and ventricular contractions and simultaneous blood pressure record.

Traction with compression of the enclosed artery and vein produces cyanosis of the ventricle, increase in size of the vein with definite anemia of part of the ventricle, closely followed by a definite increase in volume of the ventricle, later of the auricle. There is a definite fall of blood pressure amounting from 30 to 50 mm. of Hg. Removal of the left stellate ganglion in 2 dogs had no evident effect. After section of the vagi there is no fall in blood pressure.

Summary: 1. Compression of the coronary vessels and immediately adjacent tissue as described caused pain without exception, sometimes salivation, vomiting in one case, a disturbance of respiration, "acute dilatation" of the heart and various changes in the electrocardiogram. Symptoms have not been produced by localized compression and tearing of the myocardium or pericardium. This may be due to a high threshold of problematical pain endings in the normal cardiac muscle and pericardium.

2. Severance of the vagi has not interfered with transmission of pain impulses in 2 dogs.

3. Removal of the left stellate ganglion has prevented the transmission of pain impulses in 2 dogs but salivation occurred in one of the 2.

4. A prompt fall of blood pressure occurred in all acute experiments on compression of the coronary vessels as described. Section of the vagi usually prevented this fall in blood pressure.

5. Fall of blood pressure, cardiac dilatation and cardiac irritability are increased by moderate cyanosis (anoxemia).

4100

Source of the Testicular Hormone.

R. M. OSLUND.

From the Department of Physiology, University of Illinois College of Medicine.

In 1903 Ancel and Bouin[1] published the theory that the interstitial cells of the testis (the cells of Leydig) produced the testicular hormone. The theory was based upon 4 main premises, as follows: Animals remain sexually active (a) after vasectomy, (b) when they possess only cryptorchid testes, (c) when their testes have been exposed to Roentgen rays and (d) when the only testicular tissue they possess is a graft. Under each of these conditions *all* germinal epithelium was reported absent while the interstitial cells were normal or hypertrophied. All 4 of these premises have been shown to be incorrect (see Oslund[4, 5, 6, 7]) and some germinal epithelium usually exists under each of the above conditions. Since both germinal epithelium and interstitial cells are present in hormone producing testes it has seemed impossible to designate which of these produces the hormone.

It occurred to the writer that if a potent extract could be obtained from the epididymis this would offer strong presumptive evidence that the germinal portion of the testis produced the hormone. The epididymis has no interstitial cells but has a large amount of material of germinal epithelial origin. An attempt was made to obtain such an extract using McGee's method.[3] The results were doubtful, though not entirely negative.

Another point of attack seemed open. Smith[8] has shown that injection of fresh tissue will (in the case of the hypophysis) produce results simulating that of injecting the hormone. This method seemed hopeful. Fresh sperm from the *vas deferens* or epididymis was injected into 3 caponized cockerels. Positive comb growths were obtained. When the injections were discontinued resorption of the comb followed. Injection of approximately the same amounts of testicular tissue gave no observable results. The spermatic material was obtained from dogs and sheep.

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[1] Ancel and Bouin, *Arch. d. Zool. Exp.*, 1903, i, 437.

[4] Oslund, *Am. J. Physiol.*, 1924, lxvii, 422.

[5] Oslund and Bachem, PROC. SOC. EXP. BIOL. AND MED., 1926, xxiii, 761.

[6] Oslund, *Am. J. Physiol.*, lxxvii, 76.

[7] Oslund, XII International Congress of Physiology, Stockholm, 1926.

[3] McGee, Prac. Inst. of Med. of Chicago, April, 1927.

[8] Smith, *Am. J. Physiol.*, 1927, lxxx, 114.

Considerable toxicity was seen following the injection of these proteins, which interfered with the results. Another difficulty was encountered in obtaining constant amounts of the pure spermatic fluids. The difficulties encountered made the obtaining of decisive data impossible at this time. Improved extraction technique would seem to offer the best method of attack upon this problem.

The results are suggestive and point definitely to the germinal epithelium as the source of the testicular hormone. Humphrey[2] has found tissue changes that indicate that the hormonal effects first appear at the time that the spermatids are formed.

This author, therefore, points to a particular stage in the cell cycle in which the hormone is produced. Confirmatory evidence is also found in some vasectomy experiments. When the *vas deferens* is ligated the spermatic fluid must all be absorbed into the vascular or lymph system. In this way, one can account for part of the increased sex activity sometimes seen after vasectomy.

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[2] Humphrey, personal communication, 1927.

Peking Branch.

Peking Union Medical College, May 10, 1928.

4101

Studies on Auto-Digestion. IV. Antitrypsin and Clotting Time.

H. NECHELES AND MAO-KENG CHU.

From the Department of Physiology, Peking Union Medical College.

In a previous paper (Necheles, Ling and Fernando) we stated, that the trypsin inhibiting factor of the serum is not an antibody and that the survival of living tissue exposed to the action of trypsin[1] does not depend upon immunization against the ferment, but on some unknown factor.

In the course of this previous work we were struck by the fact that delayed clotting of the blood was frequently associated with a high "antitryptic" titer. We therefore tested in a series of experiments the possible relationship between clotting time and "antitryptic" titer.* The clotting time and "antitryptic" titer of the blood of 2 normal dogs (No. 870, 9.7 kg., and No. 871, 9 kg.) was determined. The blood was withdrawn daily (in the morning) by heart puncture from the left ventricle (a paraffined syringe and needle was used†). The dogs were fed in the afternoon; the food consisted mainly of carbohydrates. In the course of a week, the clotting time varied from 7′ 30″ to 13′ and the "antitryptic" titer from 0.2-0.4 in dog 870, and from 7′ 15″ to 11′ 30″ and 0.2-0.4 in dog 871, but no relationship could be found between these 2 values. There was no difference between the "antitryptic" titer of blood which had clotted in plain and that in paraffined glass tubes, although there were differences of 30 to 100% in clotting time. Blood

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* The same methods as previously described were used.[3, 5]

[1] Necheles, H., Ling, J., and Fernando, F., *Am. J. Physiol.*, 1926, lxxix, 1.

† Occasionally venous blood was drawn, which clotted much quicker; its "antitryptic" titer was not different from the average titer of arterial blood.

We are very much indebted to Dr. C. A. Mills for his kind help in determination of clotting times.

in paraffined glass tubes to which tissue fibrinogen was added clotted about 10 times quicker than the control but had the same "antitryptic" titer.

In order to see whether increasing metabolism would influence clotting time and titer, both dogs were treated with subcutaneous injections of thyroxin, till pulse rate and body temperature indicated full action of this drug. In dog 870 there were insignificant variations of the titer between 0.3 and 0.5 and no change of clotting time. In dog 871 the titer went up from 0.3 to 20.0‡ without change in clotting time. This experiment confirms our former statement about the inconsistency of changes of the "antitryptic" titer.[2]

Since running produces decrease of clotting time, 6 experiments with exercise were carried out on 4 dogs. After 10 minutes running there was in all cases a marked hastening of clotting; in one case there was a decrease of the titer (from 0.3 to 0.1) in another case an increase (from 0.3 to 0.6), in the other experiments the changes were insignificant.

In one apparently normal (starving) dog we found free trypsin in the serum. Unfortunately the animal was killed the next day, but the autopsy did not show anything peculiar; this is confirmatory of statements made by other authors.[2, 3, 4] Meat meals were found to decrease the titer down to zero in dogs; a fat meal brought it down from 0.5 to 0.1, while carbohydrate (rice) was without influence. The changes in the clotting times after the different meals were in no apparent relationships to the varying titers.

There is no relationship between "antitryptic" power of the serum and clotting time of the blood. The inconsistency of changes of the "antitryptic" titer is confirmed.

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‡ The "antitryptic" power of serum with a titer higher than about 1.0 is obtained by multiplying the titer with the degree of serum dilution. Since this procedure assumes a linear relationship between serum concentration and titer, we determined the titer in various dilutions of the sera of 3 different normal dogs. It was found that somewhat above 2% serum concentration the titer did not increase but remained constant; this was apparently due to absorption of the trypsin by the serum proteins. Below a certain dilution of the sera (1.35-0.8%) there was no more "antitryptic" action; this is apparently the lower limit of exactness of the test. Between 0.8-2% the relationship between serum concentration and "antitryptic" power was a direct one. Our calculation of the titer (here and in previous articles[2]) in sera with a very high "antitryptic" power is thus only an approximate one.

[2] Necheles, H., and Fernando, F., *Am. J. Physiol.*, 1926, lxxix, 9.

[3] Jochmann, G., and Kantorowicz, A., *Z. f. klin. Med.*, 1908, lxvi, 153.

[4] Müller, E., and Jochmann, G., *Munch. med. Wchnschr.*, 1906, liii, 2002.

4102.

Is Thrombin an Enzyme?

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From the Department of Medicine, Peking Union Medical College, Peking, China.

The earlier work on blood clotting, from the time of Schmidt,[1] was done mainly on the assumption that thrombin was an enzyme (fibrin ferment). The first seemingly definite evidence that it was not an enzyme was offered by Rettger[2] and later by the more careful work of Howell.[3] These 2 authors presented data showing a rather definite combining ratio between thrombin and blood fibrinogen when minimal amounts of the former were present. Howell raised a doubt as to the interpretation of the data, however, when he described the formation of repeated crops of fibrin in the serum following the removal of the fibrin masses, upon the weight of which they had based their first conclusions. He himself likened this behavior of thrombin to an enzyme, but still leaned toward the belief that it probably was not such. We have extended Howell's observations and obtained striking results which we briefly summarize below.

To fresh, clear, citrated dog plasma was added $(NH_4)_2SO_4$ sufficient to give 1/7 saturation and the precipitated fibrinogen filtered off, repeatedly washed in 20% NaCl, dissolved in 0.5% sodium citrate solution, reprecipitated with $MgSO_4$, washed and finally redissolved in 0.5% sodium citrate solution again. To the plasma, after the removal of the fibrinogen, $(NH_4)_2SO_4$ was further added to ½ saturation, and the precipitate collected and pressed free of liquid on a filter. This precipitate was stirred into 30% $MgSO_4$ solution, filtered, and the filtrate saturated with $MgSO_4$. The precipitate formed in this last step was collected and pressed free of as much liquid as possible. On treatment with cephalin and calcium it yielded very active thrombin, which deteriorated only slightly during 5 weeks of observation. The portion of the $(NH_4)_2SO_4$ precipitate that was insoluble in 30% $MgSO_4$ was found to contain little prothrombin.

Using these stable solutions of thrombin and fibrinogen we found that one part of thrombin might convert as high as 1,000 parts of fibrinogen to fibrin provided the fibrin was removed in successive crops. Furthermore, the clots formed exhibited the appearance of syneresis after 2 to 3 days at room temperature, but on weighing the fibrin at such times it was found that the process was really one of solution. To rule out bacterial action as a cause of the solution of the clots, we sterilized the thrombin and fibrinogen solutions before mixing by passing through a Berkefeld filter and kept the mixtures sterile throughout the period of observation. Under such conditions the clots again showed resolution after 2 to 4 days, those containing most thrombin and clotting most quickly also redissolving most rapidly. The resolution was complete, the fluid being clear and sparkling.

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[1] Schmidt, A., *Arch. ges. Physiol.*, 1875, xi, 515.

[2] Rettger, J. L., *Am. J. Physiol.*, 1909, xxiv, 406.

[3] Howell, W. H., *Am. J. Physiol.*, 1910, xxvi, 453.

Examination of the sterile fluids containing the redissolved clots showed no fibrinogen coagulating at 55° C., as did the original fibrinogen solution, but instead a heavy coagulum at 75° C. No further change took place on heating to boiling. On comparing this fluid with that from a similar mixture from which the fibrin was removed before it had begun to dissolve, it was found that the coagulum at 75° C. represented in the main the redissolved fibrin. There was no increase in the non-protein nitrogen during this resolution, so that the change was not a digestive proteolysis.

We conclude, therefore, that there are 2 phases to thrombin action, the first being a union with, and precipitation of, the fibrinogen, while the second involves a resolution of this clot with the conversion of fibrinogen into a protein of quite different behavior, coagulating at 75° C. instead of 55° C., and being resistant to further thrombin precipitation. Whether this resolution phase of thrombin action is responsible for the apparent syneresis of clots is a question we are now investigating.

4103

Production of Sugar by Surviving Liver.

A. CARRUTHERS. (Introduced by Hsien Wu.)

From the Department of Biochemistry, Peking Union Medical College.

That the liver can form carbohydrate from certain metabolites, and, in particular, lactic acid, is a view widely accepted. Examination of the experimental evidence nevertheless reveals a large number of contradictory results.

Mandel and Lusk[1] showed that lactic acid when given to the diabetic organism was excreted as glucose. This transformation they suggested occurred in the liver. Jannsen and Jost[2] could not show that intravenous injection of lactic acid led to the formation of sugar in the muscles. They supposed the change occurred in the liver. Meyerhof and Lohmann[3] and Takane[4] claim that liver slices bring about a synthesis of carbohydrate when respiring in Ringer solution containing lactic acid. Abramson and Eggleston[5] find, however, that the intact anesthetized dog does not demonstrably synthesize glycogen (in the liver) from sodium r-lactate. Finally, Burn and Marks[6] by perfusing livers previously rendered glycogen free found that there was a production of sugar which was not derived from either lactic acid or from protein. The following results were obtained in some work planned to investigate lactic acid, carbohydrate relationships in normal and abnormal tissues.

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[1] Mandel, J. A., and Lusk, G., *Am. J. Physiol.*, 1906, xvi, 129.

Rabbits were starved for 36-48 hours. The animals were stunned by a sharp blow on the head and rapidly bled to death. The liver was excised, chopped with scissors into pieces only fine enough to allow of good sampling (the tissue was not made into a brei), and samples weighed out, fairly accurately, but rapidly. The tissue to be incubated was placed in flasks containing 20 cc. phosphate-Ringer solution—pH 7.4—and the air in the flasks was displaced by oxygen. The tissue was incubated at 37° C. for 3 hours, the flasks being gently shaken all the time. The control samples were placed in either ice-cold 95% alcohol (for glycogen, soluble sugar and lactic acid determinations) or in ice-cold 4% HCl (for the total sugar content). Glycogen was estimated by Pflügers' method; soluble sugars were extracted in 66% alcohol and, after removal of the alcohol, the aqueous mixtures were cleared by the use of the $HgNO_3$ reagent of Patein and Durfan. After removal of excess mercury by H_2S and blowing off of the H_2S crystal clear solutions were obtained. To insure that there was no sugar in the tissue which escaped detection in these methods, samples were also hydrolyzed with 4% HCl for 3½ hours. After removal of proteins by NaOH and $ZnSO_4$ these solutions were also cleared with $HgNO_3$. The method of Hagedorn and Jensen was employed for the estimation of sugar.

The results in Table I show that when the total sugar content of tissue is determined by summing glycogen and soluble sugar frac-

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[2] Jannsen, S., and Jost, H., *Z. Physiol. Chem.*, 1925, cxlviii, 41.

[3] Meyerhof, O., and Lohmann, K., *Biochem. Z.*, 1926, clxxi, 381.

[4] Takane, R., *Biochem. Z.*, 1926, clxxi, 403.

[5] Abramson, H. A., and Eggleston, P., *J. Biol. Chem.*, 1927, lxxv, 763.

[6] Burn, J. H., and Marks, H. P., *J. Physiol.*, 1926, lxi, 497.

TABLE I.
Carbohydrate content estimated as glycogen and soluble sugars in mg. glucose per 5 gm. liver.

Exp. No.	Before Incubation.			After Incubation.			Difference
	Calcul'd as glucose		Total	Calcul'd as glucose		Total	
	Glycogen	Soluble sugar		Glycogen	Soluble sugar		
2	7.7 7.0	8.9 7.8	16.6 14.8	3.4	28.9	32.3	16.6
3	51.5 52.3	74.4 75.4	125.9 127.7	7.1	132.3	139.4	13.6
4	65.3 68.0	68.8 63.6	134.1 131.6	8.5 10.5	140.9 137.9	149.4 148.4	16.1

TABLE II.
Carbohydrate content estimated after acid hydrolysis in mg. glucose per 5 gm. liver.

Exp. No.	Before Incubation	After Incubation	Difference
1	96.3	100.7	+4.4
2	68.3	75.6	+7.3
4	173.8 168.1	171.4	+0.5
5	113.2 115.2	112.8	—1.4

tions (both expressed as glucose) there is apparently a production of sugar during the period of incubation. The results given are typical of what has been observed many times. With large amounts of tissue the differences may be quite considerable. Precisely why there is the difference it is difficult to say, but that it cannot be due to experimental error is suggested by the agreement between the duplicates.

That the production of sugar is only apparent and not real is shown by the results in Table II. The values given by acid hydrolysis of whole tissue show no production of sugar during incubation. It has always been found that the acid hydrolysates give a much higher value than the sum of glycogen and soluble sugar, and this is probably due to the presence of substances influencing the reducing power of the sugar. This discrepancy, however, does not invalidate the results since the agreement between the duplicates is again of a good order.

It is suggested then that when the power of the liver to produce sugar is being investigated it is not sufficient simply to estimate the sugar in terms of glycogen and soluble sugar. Acid hydrolysis of the whole tissue should also be considered.

4104

Composition of Antigen-precipitin Precipitate.

HSIEN WU, LAN-HUA CHENG AND CHEN-PIEN LI.

From the Departments of Biochemistry and Pathology, Peking Union Medical College.

Practically nothing is known about the composition of the antigen-precipitin precipitate beyond the fact that the amount of the precipitate produced may be much more than the amount of the antigen used.[1] Just how much of the antigen is present in the precipitate does not seem to have been determined. This is due to the fact that there exists no chemical method of determining the antigen (protein) and the precipitin (protein) separately.

One of us has worked out a method for the determination of minute amounts of hemoglobin.[2] The method is based on the benzidine reaction, and as little as 0.02 mg. hemoglobin suffices for a quantitative determination. When hemoglobin is used as the antigen its amount in the antigen-precipitin precipitate can be determined directly by means of that method. The amount of the precipitin in the precipitate can be determined by the difference between the total protein and the hemoglobin. The assumption is here made that the precipitate contains only the antigen and the precipitin and no other protein.

The word hemoglobin is used here in the generic sense, including oxyhemoglobin and its immediate derivatives. Oxyhemoglobin on standing is slowly converted into methemoglobin. This is, however, a matter of no consequence since oxyhemoglobin and methemoglobin have the same immunological properties[3] as well as the same chemical properties utilized for their quantitative determination in the above mentioned method.

Sheep oxyhemoglobin solution was prepared from washed cells by laking with 4 volumes of water and shaking with 2.5% suspension of freshly prepared aluminium hydroxide. The mixture was centrifuged and the clear supernatant liquid was filtered through a Seitz filter. Dog's oxyhemoglobin solution was prepared from crystals obtained by electrodialysis according to the method of Stadie.[4] Alumina cream was also used. The final solutions contained about 5% hemoglobin.

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[1] Wells, H. G., "The Chemical Aspects of Immunity," The Chemical Catalog Co., New York, 146.

[2] Wu, H., *J. Biochem.* (Japan), 1923, ii, 189.

[3] Heidelberger, M., and Landsteiner, K., *J. Exp. Med.*, 1923, xxxviii, 561.

[4] Stadie, W. C., *J. Biol. Chem.*, 1926, lxviii, 229.

For the immunization of rabbits, we have tried different procedures, but none has been found to be thoroughly satisfactory. Only 15 out of about 50 rabbits gave usable sera. This is undoubtedly due to the generally recognized weak antigenic property of hemoglobin. The last few rabbits were immunized by giving 10 or more subcutaneous injections at intervals of 3 days. Each dose was 4 cc. of 5% hemoglobin solution. The sera were tested on the 4th day after the last injection.

After a preliminary precipitin reading, suitable amounts of serum were measured into graduated centrifuge tubes and equal volumes of hemoglobin solution of different concentrations were added. The solutions were mixed by gentle rotation and left in the cold room for 24 hours. The tubes were then centrifuged and the supernatant liquid carefully decanted. The precipitate was washed with 0.9% NaCl, stirring gently with a slender glass rod, centrifuged and the supernatant liquid decanted. The washing was repeated once more. The precipitate was then dissolved in 2-3 cc. distilled water with the addition of 1 to 2 drops of 1-N Na_2CO_3. The solution was then diluted to such volume that its tint matched approximately that of a standard hemoglobin solution containing 0.025 mg. per cc. Weaker standard solutions of hemoglobin were sometimes used. 1 cc. portions of the solution were used for hemoglobin determination and suitable amounts were taken for total N determination. This latter determination was made by a modification of the Folin-Wu micro-method. Potassium persulphate was used to aid the digestion and the ammonia was aspirated into 1 cc. of 1/10 HCl solution before Nesslerization. The N content of the stock hemoglobin solution from which dilute solutions were prepared was also determined. The results of the last 5 experiments are shown in the accompanying table.

It will be noted that the percentage of the hemoglobin N in the total N remains approximately constant whether the concentration of the hemoglobin was high or low and whether the serum is strong or weak. The average value is about 10. In some experiments there was a tendency for the percentage to decrease when the concentration of the hemoglobin was low, but in such cases the precipitates produced were so small that analytical errors became appreciable.

It seemed very probable, therefore, that the antigen-precipitin precipitate has a constant composition and that the reaction between the antigen and the precipitin is, therefore, chemical and not merely physical or colloidal.

The assumption that the antigen-precipitin precipitate contains only the antigen and precipitin (protein) and no other protein

TABLE I.

Analyses of precipitates produced by the reaction of hemoglobin with anti-hemoglobin sera.

Rabbit No.	Antigen	Amt. Serum	Amt. Hb-soln.	Conc. of Hb-soln.	Total Hb-N used	Hb-N in ppt., mg.		Total N in ppt., mg.		Hb-N in total-N
		cc.	cc.	Mg. N per cc.	mg.	Total	per cc. serum	Total	per cc. serum	%
741	Sheep Hb.	3	3	0.189	0.567	0.029	0.010	0.305	0.102	9.64
		3	3	0.126	0.378	0.058	0.019	0.553	0.184	10.45
		3	3	0.095	0.285	0.056	0.019	0.480	0.160	11.71
		2	2	0.063	0.126	0.023	0.012	0.237	0.119	9.83
		4	4	0.021	0.084	0.042	0.011	0.418	0.105	10.05
		5	5	0.007	0.035	0.024	0.005	0.301	0.060	8.10
783	Dog Hb.	5	5	0.180	0.898	0.088	0.018	0.844	0.169	10.41
		3	3	0.120	0.359	0.068	0.023	0.666	0.222	10.13
		3	3	0.060	0.180	0.120	0.040	1.167	0.389	10.31
		5	5	0.020	0.100	0.071	0.016	0.953	0.191	8.54
		6	6	0.007	0.040	0.026	0.004	0.393	0.066	6.61
778	Dog Hb.	4	4	0.190	0.760	0.026	0.007	0.220	0.055	11.78
		3	3	0.127	0.381	0.032	0.011	0.307	0.102	10.38
		3	3	0.064	0.191	0.026	0.009	0.255	0.085	10.23
780	Dog Hb.	5	5	0.064	0.318	0.046	0.009	0.418	0.084	10.90
		5	5	0.021	0.106	0.028	0.006	0.309	0.062	9.00
		6	6	0.007	0.043	0.013	0.002	0.193	0.039	6.85
782	Dog Hb.	4	4	0.127	0.507	0.099	0.025	0.836	0.209	11.85
		4	4	0.064	0.254	0.079	0.020	0.795	0.199	9.93
		5	5	0.021	0.106	0.037	0.008	0.336	0.067	11.12

seems also justified in the light of our findings. If this were not the case, it would be difficult to explain the approximate constancy of the hemoglobin content of the precipitate.

4105

Tularemia in the Cat.

R. G. GREEN AND E. M. WADE.

From the Department of Bacteriology and Immunology, University of Minnesota, and the Division of Preventable Diseases, Minnsota State Board of Health.

The susceptibility of the cat to tularemia was considered by McCoy[1] in his original description of the disease which he later named tularemia. The infective material consisting of an emulsion of spleen of a guinea pig dead on the 5th day after inoculation, was injected into 3 young cats. The control guinea pig died. McCoy reported that the cats suffered no ill effects and when examined at necropsy on the 14th day, there was no reaction at the site of the inoculation, and no buboes had formed. He concluded it was safe to infer that cats are probably not susceptible to this infection.

In a later publication this problem was again considered by McCoy,[2] and he reported on the subcutaneous inoculation of 4 cats with large doses of an emulsion made from liver of a guinea pig dead of the disease. He stated that all cats remained well, while the control guinea pig died on the 7th day.

Cases of tularemia which have occurred in Minnesota[3] have incriminated the cat as a possible carrier of the disease, and indicate that cats sometimes acquire an active infection after eating an animal dead from tularemia.

A rabbit which was responsible for a human case of tularemia was fed to 3 cats of a household and appeared to be the cause of a serious illness lasting about a week in the 3 cats eating the carcass. A 4th cat which did not eat the infective material did not become sick.

A second human case appeared to obtain the infection of tularemia by the bite of a sick cat, the cat dying a few hours after inflicting the wound.

Because of these suggestive findings we have reinvestigated the susceptibility of the cat to tularemia by feeding infective material. A young cat was given a carcass of a guinea pig dead of tularemia, and the cat consumed the entire carcass in one day. Two days later the cat did not appear to be well, and when given a second guinea pig carcass on the 3rd day consumed only one-half of it, but finished eating the carcass on the 4th day. The following day it appeared to be well. On the 8th day the cat again consumed the entire carcass of a guinea pig dead of tularemia, and on the 13th day it consumed another infected carcass. Except for the short period following ingestion of the first pig the cat appeared to be perfectly well and would purr very vigorously upon being petted. It was chloroformed on the 18th day. Its blood gave a positive agglutination for *Bact. tularense* in a dilution of 1:80. At necropsy all organs were apparently normal.

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[1] McCoy, George W., *Pub. Health Bull.*, No. 43, April, 1911.

[2] McCoy, George W., and Chapin, Charles W., *J. Inf. Dis.*, 1912, x, 61.

[3] Occurred in the practice of Dr. E. C. Hanson, Park Rapids, Minn.

A guinea pig injected with an emulsion made from the cat liver remained well and at autopsy after 2 weeks appeared to be normal. A guinea pig injected with an emulsion made from the cat spleen died on the 6th day from tularemia.

A second cat was given a single feeding consisting of a liver from a guinea pig dead of tularemia. The cat appeared well for 4 days, when it began to show signs of inactivity. On the 5th day it did not want to be disturbed and was found dead on the morning of the 6th day. Necropsy showed enlargement of the mesenteric lymph nodes. All other organs were apparently normal. No lesions typical of tularemia could be observed in the liver and spleen. Two guinea pigs inoculated respectively with blood and spleen emulsion remained well. The guinea pig inoculated with the liver emulsion died on the 4th day with lesions typical of tularemia. A guinea pig inoculated with emulsion of mesenteric lymph nodes died on the 5th day with lesions typical of tularemia.

Of the 5 cats known to have eaten material infected with *Bact. tularense* one showed mild transient symptoms, three showed signs of serious illness lasting a week, and one died on the 6th day. The mild case and the fatal case only were available for necropsy, the organism being found in the spleen of the former and in the abdominal lymph nodes and liver of the latter. Of 11 cases of tularemia in Minnesota, one appeared to be due to a cat directly, and 2 others resulted from rabbits singled out by cats and transported to the abode of man. It appears that a cat in the woods is not only a contact carrier of tularemia, but may also be an infected carrier.

CORRECTION

On page 514, Volume XXV, No. 7, line 31, the first word within parenthesis should read *without* instead of *with.*

SECRETARY'S ANNUAL REPORT

April 1, 1927—March 31, 1928

With the steady growth of the Society it is increasingly important for the Secretary to inform the members periodically of basic facts, significant changes in policy and procedure. The following is a concise statement of such facts.

The Secretary wishes to draw attention particularly to

1. *Proposed changes in constitution.*
2. *Surplus of $2641.28 for the year.*
3. *Increase in the number of subscribers.*
4. *Increasing standards of* PROCEEDINGS.

For details see below.

The Secretary wishes to express his appreciation of the splendid cooperation given by the members.

Changes in Constitution.

With changing conditions and growth there has been a continuing endeavor to meet these changes in practice and by constitutional enactment. Hence, the changes in the Constitution in 1922, 1925, and 1928.

These constitutional changes, initiated by the New York group, have been consistently in the direction of transforming a local group into a national society by distributing nation wide the labors and responsibilities.

Comparison of 1922, 1925, *and* 1928 *Constitutions.*

Formerly the Council consisted of 5 New York members,* now there are 20. The chairman of each section is a *de facto* member of the Council.

Formerly there was but one editor; now there are eight (2 N. Y., 2 Pa., 1 Ill., 1 Minn., I Mich., 1 N. Car.).

Formerly applications for membership were considered by the Council of 5; now by Branch officers, Membership Committee of 3, and Council of 20. The proposed Constitution provides for a Membership Committee of 10, consisting of 1 member selected by each Section (Branch).

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* Plus past presidents.

Formerly only one Treasurer; now committee of 3 trustees.

Formerly one secretary; now 10 secretaries; each Branch secretary keeps records and reports all meetings, and aids in maintaining standards.

Types of Decentralization.

Federation of American Societies for Experimental Biology. Independent societies, officers, finances, journals. Federated for meeting purposes only.

Wistar Federation (Williams and Wilkins, Science Press, etc.), Independent societies, federated for economy in publication.

Journal of Dental Research. Independent societies, officers, finances. Publish in one journal. There is a General Editor and General Treasurer (in addition to each Society editor and treasurer).

Botanical Society of America. Federation of different societies in related fields. Sectional officers and general officers (including Council, Editor, Treasurer, Secretary). Federated for publication and meeting.

Society for Experimental Biology and Medicine, American Chemical Society, etc. *Regional groups* of one society, each group engaged in similar work. Sectional officers and general officers (including Council, Editor, Treasurer, Secretary). Common publication. Separate meetings. Common annual meeting.

A study of the societies listed in the Handbook of Scientific and Technical Societies and Institutes of the United States and Canada, in the Bulletin of the National Research Council, May, 1927, and correspondence with secretaries of all the Societies in any way analogous with ours is almost unanimously in favor of the type of organization proposed in the new Constitution.

The Council feels that the maximum decentralization or division of responsibility to all groups in the Society should be provided consistent with high standards and economy. This is offered in the proposed constitution. Further decentralization jeopardizes high standards and is too great a burden financially on the members.

A copy of the proposed Constitution will soon be distributed to each member.

ANNUAL MEETING OF OFFICERS AND DELEGATES OF BRANCHES.

The second annual conference of officers of the Society with the officers and delegates of Branches was held during the Federation meetings at Ann Arbor, April 12, 1928. With increasing size and diversity of the needs of the Branches it is hoped that these annual conferences will inform and unify the scattered Branches, bring about closer cooperation, and maintain highest standards within the Society.

The best type of organization for adoption in the constitution was the major topic of discussion. It was the sense of the conference that the form of organization in the proposed constitution served the best interests of the Society; that the Membership Committee should be enlarged to include one member from each Branch, excepting Peking.

COMMENT ON FINANCES.

There is a surplus for the fiscal year of $2641.28. The present surplus is due primarily to (a) decreased cost of printing. The Griffiths Press kindly consented to a reduction in cost of 15%. (b) The number of subscribers was considerably enlarged.

Whether it is best to build a reserve, or decrease the cost of dues or excess space, or grant more free reprints can best be determined after another year's experience.

CAMPAIGN FOR SUBSCRIBERS.

The Secretary circularized selected lists from the leading research and medical societies. We received 143 additional subscribers. It is hoped that members will aid in further increasing our subscription lists. This should make it possible to make considerable reductions in cost to members and authors.

MEMBERSHIP.

Members, March 31, 1927	851	
Elected to March 31, 1928	116	
	—	967
Honorary Members, March 31, 1928		8
Total		975
Resignations, year ending March 31, 1928	19	
Deaths, year ending March 31, 1928	8	
Dropped for arrears, year ending March 31, 1928	4	
	—	31
Net membership		944

SUBSCRIPTIONS.

Subscriptions, March 31, 1927	214	
March 31, 1928		357

Free subscriptions, March 31, 1927	31	
March 31, 1928		7
Exchange subscriptions, March 31, 1927	18	
March 31, 1928		8
Total, March 31, 1928		372
Total No. of PROCEEDINGS distributed March 31, 1927		1122
March 31, 1928		1316

OFFICERS.

President: Stanley R. Benedict.

Vice-Pres.: Peyton Rous.

Secy.-Treas.: A. J. Goldforb.

Council: O. F. Avery (1929), Robert Chambers (1929), A. E. Cohn (1930), A. F. Hess (1930), W. W. Palmer (1931), H. D. Senior (1931).

Past Presidents: F. B. Wilson, Simon Flexner, F. S. Lee, T. H. Morgan, James Ewing, Graham Lusk, William J. Gies, Gary Calkins, George B. Wallace, James W. Jobling.

Nominating Committee: A. J. Carlson, E. F. DuBois, P. J. Hanzlik, A. F. Hess, L. B. Mendel, V. C. Myers, H. C. Sherman, Donald VanSlyke, G. B. Wallace.

Editorial Committee: Present members are A. J. Carlson, B. M. Duggar, M. H. Jacobs, John Kolmer, H. B. Lewis, W. deB. MacNider, A. M. Pappenheimer, A. J. Goldforb.

Membership Committee: Present members are E. A. Doisy, Robert Chambers, I. Greenwald.

Financial Committee: Present members are William J. Gies, William H. Park, A. J. Goldforb.

PAST OFFICERS.

Date	*President*	*Vice-Pres.*	*Secy.*	*Treas.*
1903-04	Melzer	Park	Gies	Calkins
1904-05	Melzer	Ewing	Gies	Calkins
1905-06	Wilson	Dunham	Gies	Calkins
1906-07	Flexner	Dunham	Gies	Calkins
1907-08	Flexner	Morgan	Gies	Calkins
1908-09	Lee	Morgan	Gies	Lusk
1909-10	Lee	Gies	Opie	Lusk
1910-11	Morgan	Gies	Opie	Lusk
1911-12	Morgan	Levene	Wallace	Lusk
1912-13	Ewing	Levene	Wallace	Norris
1913-14	Ewing	Field	Jackson	Norris
1914-15	Lusk	Gies	Jackson	Murlin

			Secy-Treas.
1915-16	Lusk	Calkins	Jackson
1916-17	J. Loeb	Gies	Jackson
1917-18	Gies	Auer	Jackson
1918-19	Gies	Auer	Jackson
1919-20	Calkins	Wallace	Jackson
1920-21	Calkins	Wallace	Jackson
1921-22	Wallace	Jobling	Jackson
1922-23	Wallace	Jobling	Myers
1923-24	Jackson	Jobling	Goldforb
1924-25	Jackson	Jobling	Goldforb
1925-26	Jobling	Benedict	Goldforb
1926-27	Jobling	Benedict	Goldforb
1927-28	Benedict	Rous	Goldforb

BRANCHES.

Illinois.

Chairman: A. B. Luckhardt. Sec'y: W. F. Petersen. Members: 70.
Meetings: Michael Reese Hospital, October 25, 1927.
Billings Hospital, December 20, 1927.
Northwestern University Medical School, February 28, 1928.
University of Illinois, April 24, 1928.
City Club, Chicago, May 25, 1928.

Iowa.

Chairman: W. W. Swingle. Sec'y: H. A. Mattill. Members: 21.
Meetings: University of Iowa, November 2, 1927.
University of Iowa, February 1, 1928.
University of Iowa, March 25, 1928.
University of Iowa, April 30, 1928.

Minnesota.

Chairman and Secretary: F. H. Scott. Members: 42.
Meetings: University of Minnesota Med. School, October 26, 1927.
University of Minnesota Med. School, Feb'y 29, 1928.
University of Minnesota Med. School, March 27, 1928.
University of Minnesota Med. School, April 25, 1928.
University of Minnesota Med. School, May 31, 1928.

Missouri.

Chairman: John Auer. Sec'y: P. A. Shaffer. Members: 38.
Meetings: St. Louis Univ. School of Medicine, November 16, 1927.
Washington Univ. School of Medicine, Jan'y 18, 1928.
St. Louis Univ. School of Medicine, Feb'y 29, 1928.
Washington Univ. School of Medicine, May 16, 1928.

New York.

Chairman: S. R. Benedict. Sec'y: A. J. Goldforb. Members: 605.
Meetings: Post Graduate Hospital, October 19, 1927.
Rockefeller Institute, November 16, 1927.
College of Physicians and Surgeons, December 21, 1927.
Cornell University Med. College, January 18, 1928.
Presbyterian Hospital, February 15, 1928.
University and Bellevue Med. Coll., March 21, 1928.
College of the City of New York, April 18, 1928.
Yale University, May 19, 1928.

Pacific Coast.

Chairman: William Ophüls. Sec'y: T. D. Beckwith. Members: 69.
Meetings: University of California Faculty Club, October 15, 1927.
Stanford University School of Medicine, Dec. 14, 1927.
University of California Hospital, February 15, 1928.
Stanford University, April 28, 1928.

Peking (China).

Chairman: Hsien Wu. Sec'y: R. H. F. Sia. Members: 15.
Meetings: Peking Union Medical College, November 3, 1927.
Peking Union Medical College, February 9, 1928.
Peking Union Medical College, May 10, 1928.

Southern.

Chairman: W. Denis. Sec'y: W. H. Harris. Members: 22.
Meetings: Tulane University, December 13, 1927.
Tulane University, February 28, 1928.
Tulane University, May 22, 1928.

Western New York

Chairman: J. B. Sumner. Sec'y: H. S. Liddell. Members: 44.
Meetings: Cornell University, October 15, 1927.
Clifton Springs Sanitarium, December 17, 1927.
University of Buffalo, February 11, 1928.
University of Rochester, May 12, 1928.

Wisconsin.

Chairman: A. S. Loevenhart. Sec'y: F. L. Hisaw. Members: 18.
Meetings: University of Wisconsin, April 30, 1928.

New Branches.

The application of the Wisconsin members to form a Branch of the Society was approved. This makes the tenth Branch.

DEATHS OF MEMBERS.

The Council records with regret the death of the following members: D. H. Dolley, G. A. Friedman, Holmes C. Jackson, K. K. Koessler, S. A. Matthews, Francis W. Peabody, Charles E. Simon, Abraham Zingher.

GIFTS.

The Secretary wishes to acknowledge, with the thanks of the Council, the receipt of back numbers by gift from Drs. William N. Berg, H. C. Bazett, S. C. Brooks, M. M. Brooks, Vernon Kellogg, Robert L. Levy, William F. Petersen.

The Society has become affiliated with the Biologic Union and with the American Association for the Advancement of Science.

Comments, criticisms, and suggestions of members are earnestly requested.

EDITOR'S ANNUAL REPORT

April 1, 1927—March 31, 1928

There have been many expressions of appreciation of the higher standard of publication.

This is in part due to the fact that the Board of Editors have more carefully examined manuscripts than heretofore and to the fact that authors have cooperated in withdrawing duplicate and trivial manuscripts and have revised manuscripts when called upon to do so.

There were 425 papers published, of which *60% were Preliminary and 40% Complete.*

With this increase in standards there has been no increase in the size of the volume. Volume 22 contained 619 pages; Volume 23, 900 pages; Volume 24, 1004 pages, and Volume 25, 900 pages approximately.

The problem is how to get authors to state their findings in sufficiently *concise form and in such a manner that the significance of their results may be understood by colleagues in allied fields.*

TREASURER'S REPORT

April 1, 1927 to April 1, 1928

Receipts.

Income, 1927-28—		
Dues	$4814.95	
Reprints	2174.07	
Excess space	1734.27	
Author's changes, bank interest, and misc.	136.08	
Cuts	547.75	
Subscriptions	2538.06	
Back numbers	571.95	
Total annual income		$12,517.13
Special Receipts—		
Endowment Fund contributions	242.12	
Annual interest of Endowment Fund	473.89	
Total		716.01
Cash balance, April 1, 1927		1,623.98
Total cash available, April 1, 1927, to April 1, 1928		$14,857.12

Disbursements.

Publication Costs of Proceedings—		
Printing	$4253.96	
Reprints	2330.96	
Cuts	577.21	
		$ 7,162.13
Administrative Expense—		
Office supplies and postage	772.95	
Salaries	2100.90	
Storage and insurance	89.59	
Miscellaneous	51.28	
Purchase of back numbers	6.00	
Refunds	15.67	
		3,036.39
Total annual disbursements		$10,198.52
Transferred to Endowment Fund		716.01
Transferred to Life Membership Fund		75.00
Cash balance, April 1, 1928		3,867.59
Total cash available during 1927-28		$14,857.12

Summary.

Income (net)	$12,517.13	
Disbursements (net)	10,198.52	
Surplus for year		$ 2,318.61
Bills payable	none	
Bills collectable, April 1, 1928	$1,448.29	
Bills collectable, April 1, 1927	1,125.62	
Bills collectable in excess of last year		322.67
Total surplus for year		$ 2,641.28

The Treasurer desires to acknowledge with many thanks the extraordinary cooperation of Alexander Dolowitz, C. P. A., of New York, who volunteered the services of his staff to examine the books of the Society, who advised how the records should be kept in the most accurate and most economical way, who supervised the work of his staff, as his contribution to the Society.

Endowment Fund.

In R. R. Coop. Bldg. Loan Assn., April 1, 1927	$ 9,753.06
Contributions to April 1, 1928	242.12
Interest for year April 1, 1927, to April 1, 1928	484.01
Total, April 1, 1928	$10,479.19

Auditors' Report.

We have examined the accounts of the Society and the Treasurer's report, have checked the book entries against the totals, and have verified the bank balance.

The auditors would like to express their appreciation of the services rendered by Mr. Alexander Dolowitz, C. P. A., and the skill that he has shown in making available to the Treasurer records on which to base action. We strongly commend the system of bookkeeping that he has devised.

May 8, 1928.

Isidor Greenwald.
Walter H. Eddy.

MEMBERS' LIST (Alphabetical)

Honorary Members

Councilman, William T.	Harvard University
Halliburton, W. D.	London, England
Porter, William	Harvard University
Reichert, E. T.	University of Pennsylvania
Richet, Charles	Paris, France
Schaffer, E. S.	Edinburgh, Scotland
Von Muller, Friedrich	Munich, Germany
Welch, W. H.	Johns Hopkins University

Members

Abbott, Alexander C.	University of Pennsylvania
Abel, John J.	Johns Hopkins University
Addis, Thomas	Medical School, Stanford University
Adler, Herman M.	Juvenile Psychopathic Institute, Chicago
Albus, William R.	U. S. Department of Agriculture
Alexander, Harry L.	Washington University
Allen, Bennet M.	University of California
Allen, Edgar	University of Missouri
Allen, William F.	University of Oregon
Alsberg, Carl L.	Stanford University
Alvarez, Walter C.	Mayo Clinic
Amberg, Samuel	Mayo Clinic
Amoss, Harold L.	Johns Hopkins Hospital
Anderson, E. G.	University of Michigan
Anderson, John F.	E. R. Squibb & Son
Anderson, Rudolph J.	Yale University
Andrews, Edmund	University of Illinois
Arnold, Lloyd	Loyola University
Asher, Leon	Berne, Switzerland
Ashman, Richard	Tulane University
Atchley, D. W.	Presbyterian Hospital, New York City
Atkinson, H. V.	University of Iowa
Atwell, Wayne J.	University of Buffalo, N. Y.
Aub, Joseph C.	Mass. General Hospital
Auer, John	St. Louis University
Austin, J. Harold	University of Pennsylvania
Austin, W. C.	Loyola University
Avery, O. T.	Rockefeller Institute, N. Y. City

Baehr, George	Mt. Sinai Hospital, N. Y. City
Bagg, Halsey J.	Memorial Hospital, N. Y. City
Bailey, Cameron V.	N. Y. Post-Graduate Medical School
Bailey, Harold C.	Cornell University Medical College, N. Y. City
Baitsell, George A.	Yale University
Baldwin, W. Manning	Albany Medical College
Balls, A. K.	University of Pennsylvania
Banta, A. M.	Station for Exp. Evolution, Cold Spring Harbor, N. Y.
Banzhaf, Edwin J.	N. Y. Health Department
Barber, W. Howard	New York University Med. School
Barbour, Henry G.	University of Louisville
Bardeen, Charles R.	University of Wisconsin
Barlow, Orphus W.	Western Reserve University
Barnett, George D.	Stanford University
Barr, David P.	Washington University

Bass, Charles	Tulane University
Bast, T. H.	University of Wisconsin
Bauer, J. H.	Rockefeller Institute
Bauman, Louis	Presbyterian Hospital, New York City
Baumann, E. J.	Montefiore Hospital, N. Y. City
Baumberger, J. Percy	Stanford University
Bayne-Jones, S.	University of Rochester
Bazett, H. C.	University of Pennsylvania
Beard, H. H.	Western Reserve University
Becking, L. B.	Stanford University
Beckwith, T. D.	University of California
Belding, David L.	Boston University
Bell, E. T.	University of Minnesota
Benedict, S. R.	Cornell University Medical College, N. Y. City
Benton, Anne G.	Vassar College
Bennitt, Rudolf	Tufts College
Berg, B. N.	Columbia University
Berg, William N.	Berg Biological Laboratory, N. Y. City
Bergeim, Olaf	University of Illinois
Bergey, David H.	University of Pennsylvania
Berglund, Hilding	University of Minnesota
Bernhard, Adolph	Lenox Hill Hospital, N. Y. City
Beutner, R.	University of Louisville
Binger, Carl A. L.	Rockefeller Institute, N. Y. City
Birkhaug, Konrad E.	University of Rochester
Bishop, George H.	Clayton, Mo.
Blackfan, K. D.	Harvard Medical School
Blake, F. G.	Yale University
Blakesley, Albert F.	Station for Exp. Evolution, Cold Spring Harbor, N. Y.
Blatherwick, Norman R.	Potter Metabolic Clinic, Santa Barbara, Calif.
Blau, Nathan F.	Cornell University Medical College
Bloom, William	University of Chicago
Bloomfield, A. L.	Stanford University Medical School
Bloor, W. R.	University of Rochester
Blum, Harold F.	University of Oregon
Blumgart, H. L.	Boston City Hospital
Bodansky, A.	Cornell University
Bodine, J. H.	University of Pennsylvania
Boeck, William C.	Harvard University
Bollman, Jesse L.	Mayo Clinic
Boothby, Walter M.	Kahler Hospital, Rochester, Minn.
Boots, Ralph H.	Rockefeller Hospital
Bowen, B. D.	Buffalo General Hospital
Boyd, Julian D.	State University of Iowa
Boyd, Theo. E.	Loyola University
Boyden, E. A.	University of Illinois
Bradley, H. C.	University of Wisconsin
Brand, Irwin	Montefiore Hospital, New York City
Branham, Sara E.	University of Rochester
Brewer, Robert K.	Syracuse University
Briggs, A. P.	St. Louis University
Bronfenbrenner, J.	Rockefeller Institute, N. Y. City
Bronk, D. W.	Swarthmore College
Brooks, Clyde	University of Alabama
Brooks, Harlow	New York University
Brooks, Matilda M.	University of California
Brooks, S. C.	University of California
Broun, G. O.	St. Mary's Infirmary, St. Louis
Brown, E. D.	University of Minnesota
Brown, J. Howard	Johns Hopkins University
Brown, L. A.	University of Iowa
Brown, Wade H.	Rockefeller Institute, N. Y. City
Browne, W. W.	College of the City of New York

Bulger, H. A.	Barnes Hospital, St. Louis, Mo.
Bull, C. G.	Johns Hopkins University
Bunting, C. H.	University of Wisconsin
Bunting, R. W.	University of Michigan
Burget, G. E.	University of Oregon
Burnett, Theodore C.	University of California
Burns, Robert K., Jr.	University of Cincinnati
Burr, Harold S.	Yale University
Burrows, M. T.	Washington University
Burton-Opitz, Russell	Unity Hospital
Byrne, Joseph	Fordham University
Calkins, Gary N.	Columbia University
Cannon, Paul R.	University of Chicago
Cannon, Walter B.	Harvard Medical School
Carlson, A. J.	University of Chicago
Carpenter, Charles M.	N. Y. State Veterinary College
Carter, Edward P.	Johns Hopkins Hospital
Cash, James R.	Peking Union Medical College, China
Castellani, Aldo	Tulane University
Cattell, McKeen	Cornell University Medical College
Caulfield, A. H.	University of Toronto
Cecil, R. L.	Cornell University Medical College
Chace, Arthur F.	N. Y. Post-Graduate Medical School
Chambers, Robert	Cornell University Medical College
Chambers, William H.	Cornell University Medical College
Chen, K. K.	Johns Hopkins University
Chidester, F. E.	University of West Virginia
Child, C. M.	University of Chicago
Chittenden, R. H.	Yale University
Christian, Henry A.	Peter Bent Brigham Hospital
Christman, Adam A.	University of Michigan
Churchman, John W.	Cornell University Medical School
Churchman, R. H.	Cornell University Medical College, N. Y. City
Clark, Guy W.	Lederle Lab., Pearl River, N. Y.
Clark, P. F.	University of Wisconsin
Claussen, S. W.	Strong Memorial Hospital, Rochester, N. Y.
Clough, Harry	University of Rochester
Clowes, G. H. A.	Eli Lilly and Co., Indianapolis, Indiana
Cobb, Stanley	Harvard University Medical School
Coca, A. F.	Cornell University Medical College
Cohen, Barnett	U. S. Hygienic Laboratory, Washington, D. C.
Cohen, Martin	N. Y. Post-Graduate Medical School
Cohn, A. E.	Rockefeller Institute, N. Y. City
Cohn, Edwin J.	Harvard Medical College
Cohn, Isadore	New Orleans, La.
Cole, L. J.	University of Wisconsin
Cole, Rufus I.	Rockefeller Institute, N. Y. City
Cole, William H.	Rutgers University
Coleman, Warren	New York University Medical College
Collens, William S.	Brooklyn Jewish Hospital
Collett, Mary E.	Western Reserve University
Collier, William D.	St. Louis University
Collins, H. H.	University of Pittsburgh
Collins, Katherine R.	Spartansburg General Hospital, South Carolina
Collip, J. B.	University of Alberta
Congdon, Edgar D.	Bangkok, Siam
Conklin, E. G.	Princeton University
Cooke, J. V.	Washington University
Coombs, Helen C.	New York University Medical School
Copenhaver, W. M.	University of Rochester
Cori, Carl F.	State Institute of Malignant Diseases, Buffalo, N. Y.
Corley, Ralph E.	Tulane University

Corner, George W.	University of Rochester
Corper, H. J.	National Jewish Hospital, Denver, Colo.
Coulter, Calvin B.	Columbia University
Couret, M. J.	Tulane University
Cowan, John F.	Stanford University Medical School
Cowdry, E. J.	Rockefeller Institute, New York City
Cowgill, George R.	Yale University
Crampton, C. Ward	N. Y. Post-Graduate Medical School
Crile, George W.	Western Reserve University
Crohn, Burrill B.	Mt. Sinai Hospital, N. Y. City
Crozier, W. J.	Harvard University
Cruickshank, E. W. H.	University of Patna, Patna, India
Csonka, F. A.	U. S. Bureau Chemistry, Washington, D. C.
Cullen, Glenn E.	Vanderbilt University
Cummins, Harold	Tulane University
Cunningham, R. S.	Vanderbilt University
Curtis, G. M.	University of Chicago
Curtis, Maynie R.	Columbia University

Dack, Gail M.	University of Chicago
Dakin, H. D.	Ossining, N. Y.
Danforth, Charles H.	Stanford University
Daniel, J. Frank	University of California
Daniels, Amy L.	University of Iowa
Daniels, Farrington	University of Wisconsin
Danzer, Charles S.	N. Y. Homeopathic Medical College
Davenport, C. B.	Sta. for Exp. Evolution, Cold Spring Harbor, N. Y.
Davies, H. Whitridge	University of Leeds, England
Davis, D. J.	University of Illinois
Davison, Wilburt C.	Duke University
Dawson, James A.	Harvard University
Day, A. A.	Northwestern University Medical School
De Eds, Floyd	Hygienic Lab., Washington, D. C.
De Graf, A. C.	N. Y. University Medical School
Denis, Willey	Tulane University
Derick, C. L.	Rockefeller Institute
Detwiler, S. R.	Columbia University
Deuel, Harry J., Jr.	Cornell University Medical College
Dickson, E. C.	Stanford University Medical School
Diones, Louis	Von Ruck Research Lab., Asheville, N. C.
Dieuaide, Francis R.	Peking Union Medical College, China
Doan, Charles A.	Rockefeller Institute
Dochez, A. R.	Presbyterian Hospital, N. Y. City
Dock, William	Stanford University
Doisy, Edward A.	St. Louis University
Donaldson, H. H.	Wistar Institute, Philadelphia
Donaldson, J. C.	University of Pittsburgh
Dooley, M. S.	Syracuse University
Drabkin, D. L.	University of Pennsylvania
Dragstedt, Carl A.	Northwestern University
Dragstedt, Lester R.	Northwestern University
Draper, George W.	Columbia University
Draper, John W.	New York City
Dresbach, M.	Albany Medical College
Dubin, Harry E.	Metz Laboratories, N. Y. City
DuBois, E. F.	Cornell University Medical College
Duggar, B. M.	University of Wisconsin
Dunn, Halberg L.	Baltimore, Md.
Dunn, L. C.	Storrs Agr. Exp. Station
Dunn, Max	University of S. California
Dutcher, R. Adams	Pennsylvania State College
Duval, C. W.	Tulane University
Dye, Joseph A.	Cornell University Medical College

Eberson, Frederick C.	University of California Hospital
Ecker, E. E.	Western Reserve University
Eckles, C. H.	University of Minnesota
Eckstein, Henry C.	University of Michigan
Eddy, Walter H.	Columbia University
Edmunds, C. W.	University of Michigan
Edwards, D. J.	Cornell University Medical College
Eggston, Andrew A.	Manhattan Eye, Ear, Nose and Throat Hospital, N. Y. City
Eisberg, Harry B.	N. Y. University and Bellevue Medical College
Eisenbray, A. B.	Western Reserve University
Ellis, Max M.	Anderson, Indiana
Elsberg, Charles A.	Mt. Sinai Hospital, N. Y. City
Elser, W. J.	Cornell University Medical College
Emmel, V. E.	University of Illinois
Engle, E. T.	Stanford University
Epstein, A. A.	Mt. Sinai Hospital, N. Y. City
Erdmann, Rhoda	University of Berlin, Germany
Erlanger, Joseph	Washington University
Evans, Herbert M.	University of California
Ewing, James	Cornell University Medical College
Eyster, J. A. E.	University of Wisconsin

Faber, Harold K.	Stanford University Medical School
Fahr, George	University of Minnesota
Falk, I. S.	University of Chicago
Falk, K. George	Roosevelt Hospital, N. Y. City
Falls, Frederick H.	University of Illinois
Famulener, L. W.	St. Luke's Hospital, N. Y. City
Farmer, Chester	Northwestern University
Faust, Ernest C.	Peking Union Medical College, China
Felton, L. D.	Harvard University
Ferry, R. M.	Harvard University
Field, Cyrus W.	New York City
Fine, M. S.	Battle Creek, Mich.
Fischer, Albert	Berlin, Germany
Fischer, Martin H.	University of Cincinnati
Fish, Pierre A.	Cornell University
Fishberg, Ella H.	New York City
Fisher, Nelson F.	St. Luke's Hospital, Chicago
Fitch, C. P.	University of Minnesota
Fitz, Reginald	Peter Bent Brigham Hospital
Fitzgerald, J. G.	University of Toronto
Fleisher, Moyer S.	St. Louis University
Flexner, Simon	Rockefeller Institute, N. Y. City
Flinn, Frederick B.	Columbia University
Florence, Laura	N. Y. Homeopathic Medical School
Flournoy, Thomas	House of Mercy Hospital, Pittsfield, Mass.
Forbes, Alexander	Harvard University
Forbes, Henry	Milton, Mass.
Forkner, Claude E.	Rockefeller Institute
Fortuyn, A. B. D.	Peking Union Med. College
Foster, Goodwin L.	Northwestern University
Foster, Nellis B.	New York Hospital, N. Y. City
Frank, Robert T.	Mt. Sinai Hospital
Fred, E. B.	University of Wisconsin
Freedman, Louis	Metz Laboratory
Fridericia, L. S.	University of Copenhagen, Denmark
Frobisher, Martin, Jr.	Johns Hopkins University
Fry, Henry J.	New York University
Fulton, John F.	Harvard University
Funk, Casimir	Brussels, Belgium
Furth, Jacob	Rockefeller Institute

Gaebler, O. H.	New York City
Gager, C. Stuart	Brooklyn Botanic Garden, Brooklyn, N. Y.
Gamble, James L.	Harvard University
Garbat, Abraham L.	Lenox Hill Hospital, N. Y. City
Gardner, Leroy U.	Saranac Lab. for Study of Tuberculosis
Garrey, Walter E.	Vanderbilt University
Gaskell, John F.	Cambridge, England
Gasser, Herbert S.	Washington University
Gates, Frederick L.	Rockefeller Institute
Gay, F. P.	Columbia University
Gerard, R. W.	University of Chicago
Gesell, Robert A.	University of Michigan
Gettler, A. O.	University and Bellevue Medical College
Geyelin, Henry R.	Columbia University
Gibson, R. B.	University of Iowa
Gies, William J.	Columbia University
Githens, T. S.	Mulford Company, Philadelphia, Pa.
Givens, Maurice H.	Northwestern Yeast Co., Chicago
Glaser, Otto	Amherst College
Gold, Harry	Cornell University Medical College
Goldberg, S. A.	Bronx Hospital, N. Y.
Goldblatt, Harry	Western Reserve University
Goldforb, A. J.	College of the City of New York
Goldschmidt, Samuel	University of Pennsylvania
Gortner, R. A.	University of Minnesota
Gould, Harley N.	Tulane University
Graham, Evarts A.	Washington University
Graves, William W.	St. Louis University
Green, Robert G.	University of Minnesota
Greenberg, David N.	University of California
Greenwald, Isidor	Roosevelt Hospital, N. Y. City
Gregory, Louise H.	Barnard College, Columbia University
Greisheimer, Esther M.	University of Minnesota
Griffith, Fred R., Jr.	University of Buffalo
Griffith, Wendel	St. Louis University
Gross, Erwin G.	Yale University
Gross, Louis	Brownsville Hospital, N. Y. City
Gruber, Charles M.	Washington University
Guberlet, J. E.	University of Washington
Guenther A. E.	University of Nebraska
Gurchot, Charles	Cornell University
Guthrie, C. C.	University of Pittsburgh
Guy, Ruth A.	Peking Union Medical College, China
Guyer, Michael F.	University of Wisconsin

Hadley, Philip	University of Michigan
Hafkesbring, H. Roberta	Tulane University
Hagan, William Arthur	Cornell University
Hale, Worth	Harvard Medical School
Hall, Ivan C.	University of Colorado
Halsey, John	Tulane University
Halsey, Robert H.	N. Y. Post-Graduate Medical School
Hamburger, W. W.	Rush Medical College
Hamilton, B. K.	Children's Hospital, Boston
Hanke, Martin E.	University of Chicago
Hannon, R. R.	Strong Memorial Hospital, Rochester, N. Y.
Hansman, G. H.	State University of Iowa
Hanson, Frank B.	Washington University
Hanzlik, P. J.	Stanford University
Hardesty, Irving	Tulane University
Harris, Isaac F.	Tuckahoe, N. Y.
Harris, J. Arthur	University of Minnesota

Harris, Reginald G.	Cold Spring Harbor, N. Y.
Harris, William H.	Tulane University
Harrison, R. G.	Yale University
Harrop, George A., Jr.	Johns Hopkins University
Harrow, Benjamin	College of the City of New York
Hartman, Carl G.	Johns Hopkins University
Hartman, F. A.	University of Buffalo
Hartwell, John A.	Cornell University Medical College
Harvey, E. Newton	Princeton University
Harvey, Samuel C.	Yale University
Hastings, A. Baird	University of Chicago
Hastings, E. G.	University of Wisconsin
Hatcher, R. A.	Cornell University Medical College
Hawk, P. B.	N. Y. City
Hayden, Charles E.	Cornell University
Haythorn, Samuel R.	Singer Research Lab., Pittsburgh, Pa.
Heft, Hattie L.	Columbia University
Heidelberger, Michael	Mt. Sinai Hospital
Heilbrunn, L. V.	University of Michigan
Helff, O. M.	State University of Iowa
Helmholz, Henry R.	Mayo Clinic
Hemmeter, John C.	Baltimore, Md.
Hench, Philip S.	Mayo Clinic
Hendrix, B. M.	University of Texas
Henrici, Arthur T.	University of Minnesota
Herrman, G. R.	Tulane University
Hertzman, A. B.	St. Louis University
Hess, Alfred F.	N. Y. University and Bellevue Medical School
Heymans, J. F.	U. de Gand, Belgium
Higgins, George M.	Mayo Clinic
Hill, Eben C.	Johns Hopkins University
Hiller, Friedrich	University of Chicago
Himwich, H. E.	Yale University
Hines, H. M.	State University of Iowa
Hinshaw, H. C.	University of California
Hirschfelder, Arthur	University of Minnesota
Hisaw, F. L.	University of Wisconsin
Hitchcock, Fred A.	Ohio State University
Hoffman, George L.	Allegheny County Hospital, Pittsburgh, Pa.
Hoffman, W. F.	Cloquet, Minn.
Holm, George E.	Department of Agriculture, Washington, D. C.
Holman, Emil	Stanford University
Holman, W. L.	University of Toronto
Holmes, S. J.	University of California
Holt, L. Emmett, Jr.	Johns Hopkins University
Hooker, Davenport	University of Pittsburgh
Hooker, Sanford B.	Boston University
Hooper, Charles W.	Metz Laboratories
Hopkins, J. Gardner	Columbia University
Horsley, J. Shelton	St. Elizabeth's Hospital, Richmond, Va.
Hoskins, R. G.	Harvard University
Höst, H. F.	Horik, Norway
Howard, Harvey J.	Washington University
Howe, Paul E.	Department of Agriculture, Washington, D. C.
Howell, K. M.	Michael Reese Hospital
Howell, William H.	Johns Hopkins University
Howland, Ruth B.	New York University
Hubbard, Roger S.	Clifton Springs Sanitarium, N. Y.
Huber, G. Carl	University of Michigan
Huestis, R. R.	University of Oregon
Hunt, Reid	Harvard University
Hunter, Andrew	University of Toronto

Huntoon, F. M.	Mulford Co., Glenolden, Pa.
Hurwitz, Samuel	University of California
Hussey, Raymond	Yale University

Irving, Lawrence	University of Toronto
Irwin, Marion	Rockefeller Institute
Ivy, Andrew C.	Northwestern University

Jackson, C. M.	University of Minnesota
Jackson, D. E.	University of Cincinnati
Jackson, Henry, Jr.	Boston City Hospital
Jacobs, M. H.	University of Pennsylvania
Jacobs, Walter A.	Rockefeller Institute, N. Y. City
Jacobsen, Walter C.	Albany Medical College
Jaffe, Henry L.	Hospital for Joint Diseases, N. Y. City
Jaffe, Richard H.	University of Illinois
Jeans, Philip C.	University of Iowa
Jennings, H. S.	Johns Hopkins University
Jobling, J. W.	Columbia University
Johns, Foster M.	Tulane University
Johnson, C. A.	University of Chicago
Johnson, T. B.	Yale University
Jonas, Leon	University of Pennsylvania
Jones, Frederick S.	Rockefeller Institute, Princeton, N. J.
Jordan, Edwin	University of Chicago
Jordan, H. E.	University of Virginia
Jorstad, L. H.	Barnard Free Skin and Cancer Hospital, St. Louis, Mo.
Joseph, Don R.	St. Louis University
Joslin, E. P.	Boston, Mass.
Jungeblut, Claus	Stanford University

Kahn, Morris H.	Beth Israel Hospital, N. Y. City
Kahn, Morton C.	Cornell Medical College, N. Y. City
Kahn, R. L.	Michigan Department of Health, Lansing
Karsner, H. T.	Lakeside Hospital, Cleveland
Kast, Ludwig	N. Y. Post-Graduate Medical School
Katayama, I.	N. Y. Post-Graduate Medical School
Katz, L. N.	Western Reserve University
Keefer, Chester S.	University of Chicago
Keeton, Robert W.	University of Illinois
Keitt, G. W.	University of Wisconsin
Kellogg, W. H.	University of California
Kendall, Arthur I.	Northwestern University Medical School
Kendall, E. C.	Mayo Clinic, Minn.
Kessel, John F.	University of California
Key, John A.	Shriner Hospital, St. Louis, Mo.
Killian, J. A.	N. Y. Post-Graduate Medical School
Kingsbury, F. B.	Metropolitan Life Insurance Co., N. Y. City
Kinsella, Ralph A.	St. Louis University
Kirkbride, Mary B.	N. Y. State Dept. of Health, Albany, N. Y.
Kleiner, I. S.	N. Y. Homeopathic Medical School
Kleitman, Nathaniel	University of Chicago
Kligler, I. J.	Hebrew University, Palestine
Kline, B. S.	Mt. Sinai Hospital, Cleveland, Ohio
Klotz, Oskar	University of Toronto
Knowlton, Frank P.	Syracuse University
Knudson, Arthur	Albany Medical College
Koch, Elizabeth	University of Illinois
Koch, Fred C.	University of Chicago
Koch, Mathilda L.	Greenwich, Conn.
Kofoid, Charles A.	University of California
Kolmer, John A.	University of Pennsylvania

Kopeloff, Nicholas	Psychiatric Institute, N. Y. City
Koppányi, Theodore	Syracuse University
Korns, John H.	Olean, N. Y.
Koser, Stewart	University of Illinois
Kramer, Benjamin	Brooklyn Jewish Hospital
Krasnow, Frances	Columbia University
Krumbhaar, E. B.	Philadelphia General Hospital, Philadelphia
Krumwiede, Charles	N. Y. City Dept. of Health
Kruse, Theophile K.	University of Pittsburgh
Kugelmass, I. Newton	Yale University
Kunde, Marg.	University of Chicago
Kuntz, Albert	St. Louis University

Ladd, William S.	Presbyterian Hospital
Lamar, R. V.	University of Georgia
Lambert, R. A.	School of Tropical Medicine, San Juan
Lamson, Paul D.	Vanderbilt University
Lamson, Robert W.	Los Angeles, Calif.
Lancefield, D. E.	Columbia University
Landsteiner, Karl	Rockefeller Institute, N. Y. City
Langstroth, Lovell	University of California
Larsell, Olaf	University of Oregon
Larson, Edward	University of Alabama
Larson, J. A.	Johns Hopkins Hospital
Larson, W. P.	University of Minnesota
Lashley, K. S.	Institute for Juvenile Research, Chicago
Lathrop, Carl O.	University of Buffalo
Laughlin, H. H.	Sta. for Exp. Evolution, Cold Spring Harbor, N. Y.
Laurens, Henry	Tulane University
Leake, J. P.	Hygienic Laboratory, Washington, D. C.
Lee, Ferdinand C.	Johns Hopkins University
Lee, Frederick S.	Columbia University
Lee, Milton O.	Harvard University
Leonard, C. S.	Yale University
Levene, P. A.	Rockefeller Institute, N. Y. City
Levene, Victor	Creighton University
Levin, Isaac	New York City
Levine, Michael	Montefiore Hospital, N. Y. City
Levine, Samuel Z.	Cornell University Med. College
Levinson, Samuel A.	University of Illinois
Levy, Robert L.	Presbyterian Hospital, N. Y. City
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